Short Communication

Interstitial lung disease associated with anti-citrullinated peptide/protein antibody-positive anti-synthetase syndrome

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Abstract: Little has been reported on the characteristics of interstitial lung disease (ILD) associated with anti-citrullinated peptide/protein antibody (ACPA)-positive anti-synthetase syndrome (ASS). We sought to investigate the clinical, radiologic, and pathologic features of patients with ILD associated with ACPA-positive ASS. Medical records of seven ILD patients with positive results of both ACPA and anti-aminoacyl-tRNA synthetase antibody were retrospectively reviewed. Five patients had clinical symptoms associated with ASS other than ILD. On high-resolution computed tomography (HRCT) analysis, a nonspecific interstitial pneumonia (NSIP) pattern was shown in 3 patients and NSIP with organizing pneumonia (OP) overlap in 2 patients. Coronal slices of these 5 patients showed lower lung disease predominance with traction caudally on major fissures due to lower lobe volume loss. These were features that could commonly be observed in ASS-associated ILD. Pathological findings available for 3 patients showed NSIP. The characteristics of ILD associated with ACPA-positive ASS appear to be similar to those of ILD associated with ASS, but not to rheumatoid arthritis (RA) or ACPA, especially in terms of the radiological findings.

Keywords: Anti-synthetase syndrome (ASS); interstitial lung disease (ILD); anti-citrullinated peptide/protein antibody (ACPA); radiology

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Introduction

Assays for detecting anti-citrullinated peptide/protein antibody (ACPA) have been shown to be a very good diagnostic tool for rheumatoid arthritis (RA) due to their its high specificity (1). On the other hand, anti-aminoacyl-tRNA synthetase (anti-ARS) antibodies are the most frequently detected in anti-synthetase syndrome (ASS) (2). Most clinical manifestations of ASS are characterized by myositis [i.e., polymyositis (PM)/dermatomyositis (DM)], arthritis, mechanic's hand, interstitial lung disease (ILD), and Raynaud's phenomenon (2-4). Serological testing of autoantibodies of ILD patients is recommended to identify the high proportion of patients with connective tissue disease (CTD)-ILD with implications for diagnosis and management (5). Recently defined "interstitial pneumonia with autoimmune features (IPAF)" also emphasizes the importance of CTD-related autoantibodies (6). On the other hand, we previously suggested that each of the specific autoantibodies of IPAF may be necessary to assess

the appropriate strategy to diagnose and treat IPAF (7). The features of ILD associated with ACPA and anti-ARS were previously reported (8-10). However, even though a few cases have been reported (11-14), the clinical significance of ILD associated with ACPA-positive ASS has not yet been evaluated. Our aim was to review ILD associated with ACPA-positive ASS patients. Whether ILD associated with ACPA-positive ASS should be managed in accordance with ACPA-positive ILD or ASS-associated ILD is a large clinical question. This investigation was clinically relevant and important to determine appropriate treatment of ILD associated with ACPA-positive ASS patients.

Methods

Materials

Our study included 71 consecutive patients diagnosed with ASS-associated ILD between December 2010 and May 2016 at our hospital. These patients were carried out routine examination of ACPA. Of those, we selected 7 consecutive patients diagnosed as having ILD associated with ACPA-positive ASS. This retrospective cohort study was approved by the institutional review board of Kanagawa Cardiovascular and Respiratory Center (KCRC-17-0014). Because of the retrospective nature of the study, the review board waived the need for written informed consent from the patients.

Study methods

Baseline clinical measurements were obtained within 3 months of the initial diagnosis of ILD. ACPA was tested using chemiluminescent enzyme immunoassay testing of sera (BML Inc., Japan). A positive result for ACPA was defined as a measurement greater than 4.5 U/mL. For anti-ARS antibodies (anti-Jo-1, EJ, PL-7, PL-12, OJ, and KS antibodies), routine conserved serum of each patient at the diagnosis of ILD in Kanagawa Cardiovascular and Respiratory Center was measured by RNA immunoprecipitation and protein immunoprecipitation assays at Tokai University School of Medicine, Japan. ASS patients were defined as having one of the ARS antibodies with ILD. Two experienced thoracic radiologists (T Iwasawa and S Iso) reviewed all high-resolution computed tomography (HRCT) scans for consensus of diagnosis of ILD in our hospital without knowledge of the patients' clinical data. The HRCT pattern was based on the previous guidelines (15). Findings inconsistent with the usual interstitial pneumonia (UIP) pattern were classified into nonspecific interstitial pneumonia (NSIP), organizing pneumonia (OP), and NSIP with OP overlap (NSIP + OP) according to previous reports (16,17). NSIP + OP was identified when consolidations were superimposed on a background of ground-glass opacity (GGO) with or without reticulations or traction bronchiectasis (16). HRCT findings were analyzed from each of the characteristic viewpoints of ACPA-positive ILD (i.e., honeycombing, centrilobular nodules, bronchial wall thickening, and expiratory air trapping) and ILD associated with ASS (i.e., lower lung volume loss and lower lung predominance) referring to previous reports (9,10,16,18,19). These HRCT findings were interpreted according to the recommendations of the Fleischner Society (20). Disagreements between the two radiologists after the initial assessment were resolved by discussion. Surgical lung biopsy specimens were available from 3 patients and were reviewed by two pulmonary pathologists (K Okudela and T Takemura) who were blinded to the patients' clinical and radiologic information. Histologic patterns were classified according to the classification of idiopathic interstitial pneumonia (17,21). Disagreements between the two pathologists were discussed until consensus was reached. Treatment responses as measured by pulmonary function tests are presented as the percentage change of the initial value. Improved and Worsened were defined as >10% positive or negative changes, respectively, in forced vital capacity (FVC) or >15% in %diffusing capacity of the lung for carbon monoxide (%D_{LCO}) (22). Patients who did not meet the criteria for consideration as Improved or Worsened were considered Stable.

Results

Patient characteristics

In our cohort of ASS-associated ILD, 7 patients (9.9%) were diagnosed ILD associated with ACPA-positive ASS. A summary of the characteristics of the patients with ILD associated with ACPA-positive ASS in our study is shown in *Table 1*. Of the 7 patients, 6 (85.7%) were female, and 4 (57.1%) had a history of smoking. Median patient age was 67 years (range, 51–87 years). Anti-ARS antibodies included anti-Jo-1 in 4 patients (57.1%), anti-PL-7 in 1 (14.3%) patient, anti-KS in 1 (14.3%) patient, and anti-EJ in 1 (14.3%) patient. Clinical symptoms of ASS other

Table 1 Patient characteristics at the diagnosis of ILD associated with ACPA-positive ASS

Characteristic	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Age/sex	61/female	70/female	51/female	87/female	79/female	67/male	40/female
Smoking history	–	+	+	–	–	+	+
Anti-ARS antibody	Jo-1	Jo-1	PL-7	KS	Jo-1	EJ	Jo-1
ACPA (U/mL)	73.1	34.8	264.7	13.2	406.9	88.0	21.0
CK (IU/L)	286	389	33	42	52	139	81
Arthralgia	+	+	+	–	–	–	–
Myalgia or muscle weakness	+	+	–	–	–	–	–
Skin lesion	Mechanic's hand	Mechanic's hand	Mechanic's hand	–	Raynaud phenomenon	Mechanic's hand, Gottron's sign	–
%FVC	73.8	60.9	81.1	N/A	69.9	N/A	87.0
$\%D_{LCO}$	61.3	35.8	65.5	N/A	53.4	N/A	69.8
HRCT pattern	NSIP	NSIP + OP	NSIP + OP	NSIP	NSIP	OP	Possible UIP
Lower lobe volume loss	+	+	+	+	+	–	+
Lower predominance	+	+	+	+	+	+	+
Honeycombing	–	–	–	–	–	–	–
Centrilobular nodules	–	–	–	–	–	–	–
Bronchial wall thickening	–	–	–	–	–	–	–
Expiratory air trapping	+	–	+	–	–	–	–
Pathologic pattern	Fibrotic NSIP	N/A	Cellular NSIP	N/A	N/A	N/A	Fibrotic NSIP
Treatment	PSL + TAC	PSL + TAC	PSL + TAC	PSL + CyA	PSL + TAC	PSL + TAC	None
Treatment response of ILD	Stable (%FVC: +8.0%) ($\%D_{LCO}$: +4.1%)	Improved (%FVC: +33.0%) ($\%D_{LCO}$: +30.0%)	Improved (%FVC: +24.3%) ($\%D_{LCO}$: +21.9%)	N/A	Improved (%FVC: +4.8%) ($\%D_{LCO}$: +26.6%)	N/A	N/A
Outcome (follow-up period)	Alive (34 months)	Alive (44 months)	Alive (32 months)	Dead (54 months)	Alive (14months)	Alive (21 months)	Alive (38 months)

ACPA, anti-citrullinated peptide/protein antibody; ARS, aminoacyl tRNA synthetase; ASS, anti-synthetase syndrome; CK, creatine kinase; CyA, cyclosporine; DLCO, diffusing capacity of the lung for carbon monoxide; FVC, forced vital capacity; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; N/A, not available; NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia; PSL, prednisolone; TAC, tacrolimus; UIP, usual interstitial pneumonia.

than ILD included arthralgia in 3 patients (42.9%), myalgia or muscle weakness in 2 patients (28.6%), mechanic's hand in 4 patients (57.1%), Raynaud's phenomenon in 1 patient (14.3%), and Gottron's sign in 1 patient (14.3%). Pulmonary function test results showed a median %FVC of 73.8% (range, 60.9–81.1%) and $\%D_{LCO}$ of 61.3% (range, 35.8–69.8%).

Radiological and pathological analysis

HRCT in 5 patients (71.4%) revealed GGO or consolidation along the bronchovascular bundles, which indicated NSIP in 3 patients (cases 1, 4, 5) and NSIP + OP in 2 patients (cases 2, 3) (left panel in *Figure 1A,B,C,D,E*). Coronal slices from these 5 patients showed lower lung predominance

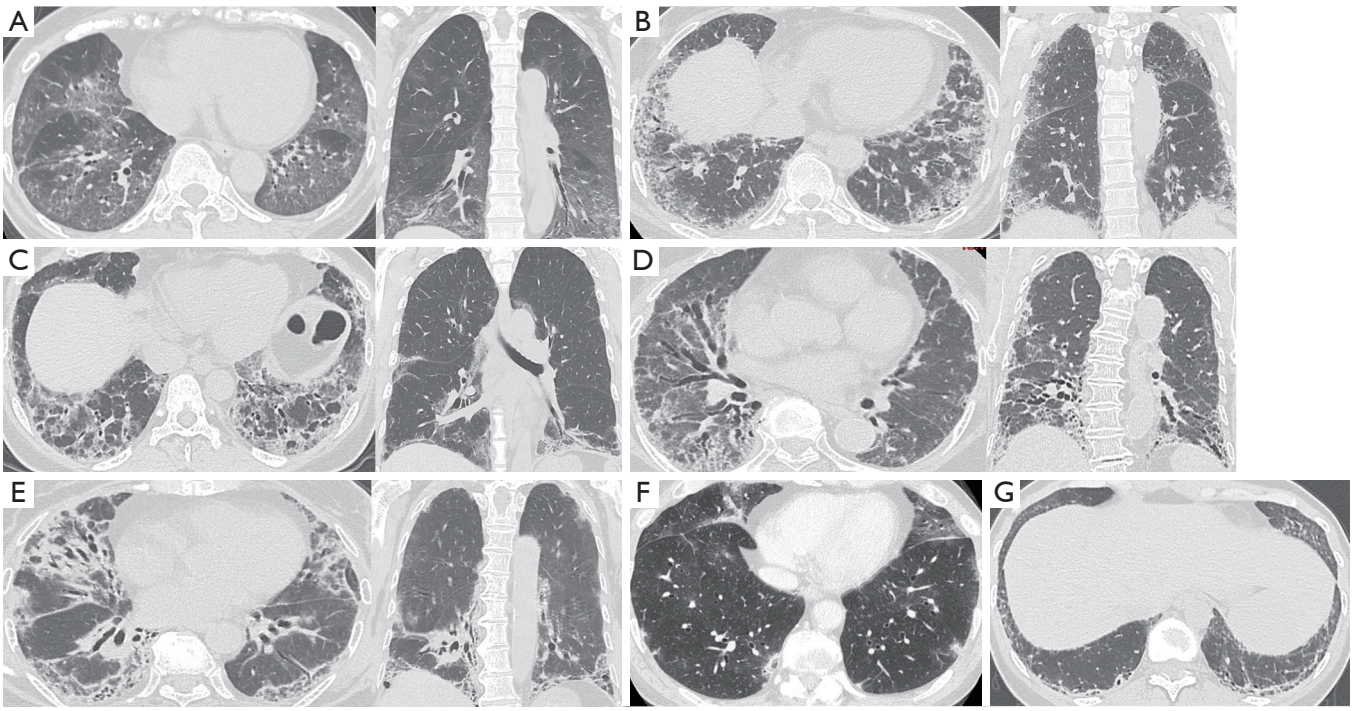

Figure 1 Chest HRCT findings of 7 patients. (A) Case 1, NSIP pattern: uniform GGO along bronchovascular bundles were distributed predominantly in the lower lung; (B) case 2, NSIP + OP pattern: mild high-attenuation lesion with traction bronchiolectasis and lower lung volume loss were seen; (C) case 3, NSIP + OP pattern: GGO with consolidation were present with extreme basilar predominance, which resulted in major fissures being dragged caudally; (D) case 4, NSIP pattern: GGO, reticulation, and lower lung volume loss along with severe traction bronchiectasis in the middle and lower lung; (E) case 5, NSIP pattern: consolidation along with traction bronchiectasis was mainly distributed, and GGO and reticulation were seen in the peripheral zone; (F) case 6, OP pattern: focal consolidations were non-segmentally present in both lungs; (G) case 7, possible UIP pattern: peripheral- and basilar-predominant reticulation without honeycombing was seen. GGO, ground-glass opacities; NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia.

and major fissures being dragged caudally due to lower lobe volume loss (right panel in *Figure 1A*,*B*,*C*,*D*,*E*). In addition, the HRCT pattern included OP in 1 patient (case 6) (*Figure 1F*) and possible UIP in the other patient (case 7) (*Figure 1G*). The pathological findings in 3 cases resulted in a diagnosis of fibrotic NSIP in 2 patients (cases 1, 7) and cellular NSIP in 1 patient (case 3) (*Figure 2*). Additionally, lymphoid follicles with cellular infiltration were also seen in 2 cases (case 3, 7). With regard to airway disease, cellular bronchiolitis were seen with NSIP in 1 patient (case 3).

Treatment response and outcome

Six (85.7%) of the patients with ILD associated with ACPA-positive ASS received anti-inflammatory drugs (prednisolone + cyclosporine or tacrolimus) within 3 months after the ILD diagnosis, and the other patient (case 7) was carefully observed. After starting therapy, muscle or joint symptoms of ASS other than ILD improved in all 3 patients. In addition, no one developed these symptoms during follow-up period. All 6 patients who received anti-inflammatory therapy showed radiological improvement of their ILD. Of the 4 patients with available pulmonary function test results during follow-up, treatment responses resulted in 3 patients being considered Improved and 1 patient being considered stable. The median follow-up period was 34 months (range, 14–56 months), during which only 1 patient (case 4) died due to chronic mild progressive ILD and old age (*Table 1*).

Discussion

From the viewpoint of radiological features, our study

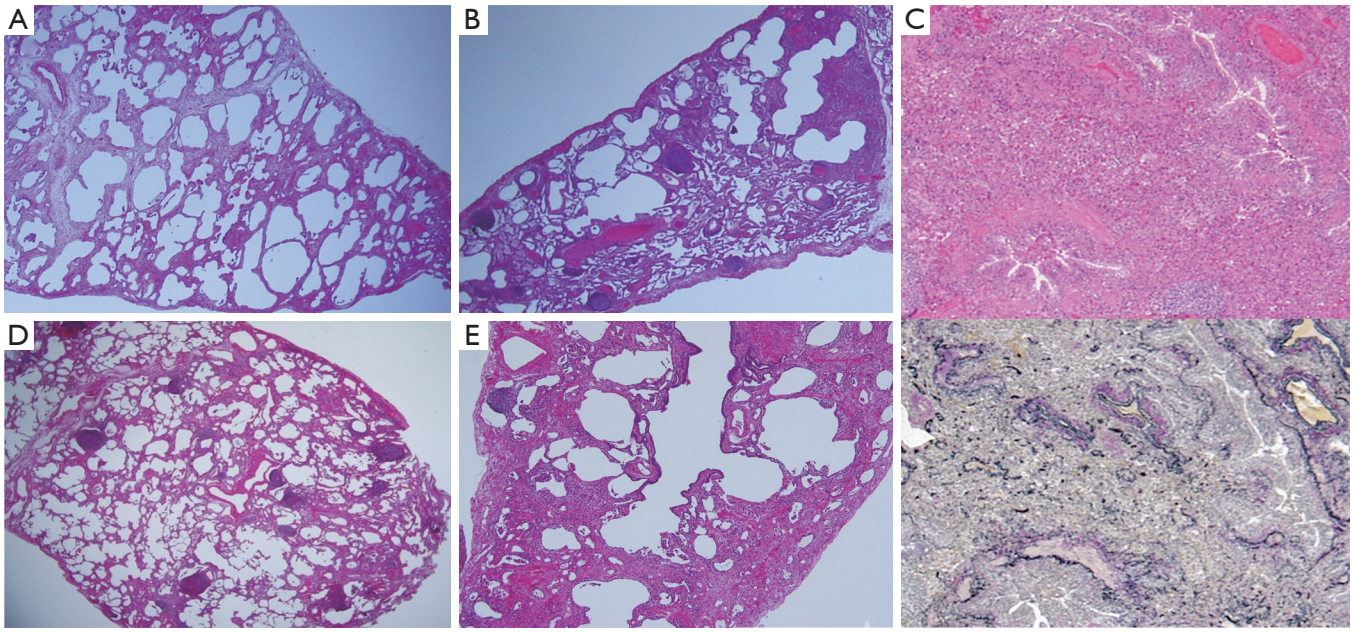

Figure 2 Pathological findings in 3 cases of ILD associated with ACPA-positive ASS. (A) Case 1, fibrotic NSIP: interstitial thickening was primarily due to uniform loose fibrosis and mild chronic inflammation. Some relatively preserved alveolar septa were present (hematoxylin-eosin stain, ×12.5); (B) case 3, cellular NSIP: pan-lobular and homogeneous pattern including interstitial cellular infiltration and organization located in the airspace or alveolar septa were seen. Some lymphoid follicles were also present (hematoxylin-eosin stain, ×12.5); (C) same patient: transmural cellular infiltrate of small round cells was present around the bronchiole. The lumen of the bronchiole was seen with destroyed bronchiolar walls (upper panel; hematoxylin-eosin stain, lower panel; elastica van Gieson stain, ×50); (D) case 7, fibrotic NSIP: chronic inflammatory cells with markedly thickened alveolar septa in the subpleural region were seen along with hyperplasia of lymphoid follicles. Fibroblastic foci were not seen (hematoxylin-eosin stain, ×12.5); (E) same patient: cystic lesions due to expansion of the airway from the respiratory bronchiole to alveolar duct were partly seen that were a result of type II pneumocystis hyperplasia and were obviously not honeycombing (hematoxylin-eosin stain, ×20). ACPA, anti-citrullinated peptide/protein antibody; ASS, anti-synthetase syndrome; ILD, interstitial lung disease; NSIP, nonspecific interstitial pneumonia.

suggested that the characteristics of ILD associated with ACPA-positive ASS may appear similar to those of ILD associated with ASS, but not those of RA or ACPA. As in previous reports of ILD associated with ASS (10,16), our patients with ILD associated with ACPA-positive ASS also showed that the most common HRCT pattern was NSIP, followed in order by NSIP + OP, possible UIP, and OP. Moreover, the patients in 3 previous case reports of ILD associated with ACPA-positive ASS presented with NSIP + OP (11,12,14) (*Table 2*). Coronal slices of our 5 cases (cases 1–5) showed lower predominance of reticulation, GGO, and traction bronchiectasis with or without consolidation, which indicated that lower lobe volume loss resulted in dragging major fissures caudally. These specific findings were reported to be characteristic of ILD associated with ASS by Fischer *et al.* (19). However, the lung phenotypic characteristics resemble those of RA-ILD and ACPA-positive ILD but not RA [8]. In RA-ILD or ILD associated with ACPA, unlike in most other CTDs, the UIP pattern is more commonly seen than NSIP (8,23). Additionally, no previous reports showed a NSIP + OP pattern in RA-ILD including ILD associated with ACPA. Only 1 patient (case 7) showed a possible UIP pattern in our study. Taken together, the results of our patients and previous case reports suggested the possibility that ACPA-positive ASS favors a characteristic radiological ILD pattern of ASS rather than ILD associated with RA or ACPA.

The most common histological pattern of CTD-ILD is NSIP (24). In contrast, the proportion of UIP pattern was reported to be higher in ILD associated with RA or ACPA followed by NSIP (8,25). Although it was previously thought in the past that lymphoid follicles are

Table 2 Summary of case reviews of ILD associated with ACPA-positive ASS

References	Age/sex	Anti-ARS antibody	ACPA (U/mL)	CK (IU/L)	Arthralgia	Myalgia or muscle weakness	Skin lesion	HRCT pattern	Pathologic pattern	Treatment	Clinical course (follow-up period)
Yamauchi *et al.* (10)	63/female	PL-7	69.0	25	+	+	NFB · PE	NSIP + OP	N/A	PSL + CyA	Improved (unknown)
Park *et al.* (11)	56/female	Jo-1	+	3755	+	+	Mechanic's hand	NSIP + OP	N/A	PSL + CPA	Improved (unknown)
Watanabe *et al.* (12)	54/female	EJ	+	N/A	+	–	–	N/A	Fibrotic NSIP	N/A	N/A
	62/male	EJ	+	N/A	+	–	Fingertip eczema	N/A	N/A	N/A	N/A
Tomioka *et al.* (13)	53/female	EJ	>100	82	+	–	–	NSIP + OP	Fibrotic NSIP	PSL + CyA	Improved (5 years)

ACPA, anti-citrullinated peptide/protein antibody; ARS, aminoacyl tRNA synthetase; ASS, anti-synthetase syndrome; CK, creatine kinase; CPA, cyclophosphamide; CyA, cyclosporine; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; N/A, not available; NFB, nail fold bleeding; NSIP, nonspecific interstitial pneumonia; PE, periungual erythema; PSL, prednisolone; OP, organizing pneumonia.

commonly seen especially in ILD associated with RA or ACPA, lymphoid follicles were a remarkable finding in ILD associated with ASS as reported by Watanabe *et al.* (13). Our previous pathological analysis of anti-EJ antibody associated ILD also showed lymphoid follicles in half of the cases (26). Our cases with available pathological findings showed NSIP with or without lymphoid follicles, and previous case reports also showed the same (*Table 2*) (13,14). On the other hand, high ACPA titer was significantly associated with small airway disease in RA subjects (18). Although only 1 patient (case 3) showed cellular bronchiolitis with ILD, coexistence of small airway disease and ILD may be meaningful in ACPA-positive ASS patients. In other words, from the viewpoint of pathological findings, we could not determine whether ILD associated with ACPA-positive ASS is closer in character to ILD associated with ASS or ACPA.

The clinical symptoms of some of the ACPA-positive ASS patients included severe arthritis, but those patients with myositis showed a good treatment response (27,28). If the patient have arthralgia or arthritis, these symptoms are hard to decide if it is either RA or ASS (28). Meyer *et al.* reported that approximately 40% of ACPA-positive ASS patients were still under prednisolone treatment at a dosage ≥10 mg/day (mean follow-up, 93.19 months) (28). None of our 3 patients (case 1–3) experienced a relapse of arthralgia under prednisolone (≤10 mg/day) during the follow-up period. Although only a few cases were analyzed, combined therapy with tacrolimus as a calcineurin inhibitor might also be effective. The reported treatment response of ILD of most patients, whether those with NSIP (including NSIP + OP) in association with ASS or CTD (e.g., RA, PM/DM) was often good as in our patients (16,21,29).

Recent guidelines recommend serologic evaluations such as rheumatoid factor, ACPA, and anti-nuclear antibody in ILD, even in the absence of signs or symptoms of CTD, provided that more specific antibodies such as anti-ARS antibodies are evaluated in select cases because of unclear diagnostic value of the other evaluations and to improve cost effectiveness (15). However, anti-TNF agents for RA may even trigger myositis and/or ILD in ASS and lead to refractory arthritis (27,30). In other words, RA therapy may lead to harmful events (including ILD) in patients diagnosed as having RA when the patient's ILD is associated with ACPA-positive ASS. Therefore, we may perform serologic tests for anti-ARS antibodies in ILD patients even if they are positive for ACPA. Particularly, special care should be taken when assessing patients with a radiological ILD pattern of ASS rather than RA or ACPA, as described above.

Our results need to be interpreted with caution due to the following limitations. First, this was a retrospective, the sample size was small, and some clinical and pathological findings were not available. Second, since ILD became the reason why our patient was diagnosed as ACPA-

positive ASS, this study was viewed from respiratory physicians, not rheumatologists. However, if the patients have autoantibodies related to CTD, we usually consult the rheumatologists to determine whether the diagnosis of CTD can be fulfilled. Third, there was selection bias because not all of the patients with ILD were evaluated for ACPA or anti-ARS antibodies, there was selection bias. However, the chest clinicians in our center carry out screening while always keeping routine examination of each antibody in mind, even if the patients with ILD have no symptoms suspicious of CTD. Therefore, we could collect rare cases of ILD associated with ACPA-positive ASS.

We conclude that despite these limitations, our study suggests that the characteristics of ILD associated with ACPA-positive ASS are similar to those of ILD associated with ASS. We believe that the results of our study will be helpful in determining the management of ILD, particularly in terms of serologic evaluation. Further studies are warranted to determine appropriate treatment of ILD associated with ACPA-positive ASS.

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Footnote

Conflicts of Interest: All work was performed at the Kanagawa Cardiovascular and Respiratory Center. The authors have no conflicts of interest to declare.

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