

## CHARACTERISTICS OF CHEST HIGH-RESOLUTION COMPUTED TOMOGRAPHY IN PATIENTS WITH ANTI-AMINOACYL-tRNA SYNTHETASE ANTIBODY-POSITIVE INTERSTITIAL LUNG DISEASE

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**ABSTRACT.** *Background and aim:* Anti-aminoacyl-tRNA synthetase (ARS) antibodies form a condition called Antisynthetase syndrome (ASSD). While interstitial lung disease (ILD) is a particularly frequent manifestation of ASSD and is closely associated with morbidity and mortality, few studies have been conducted on its characteristics on high-resolution computed tomography (HRCT). In this study, we clarified the HRCT findings in patients with anti-ARS antibody-positive ILD (ARS-ILD). *Methods:* The HRCT findings at the time of the ILD diagnosis in 24 ARS-ILD patients were retrospectively evaluated by 2 pulmonologists and one radiologist. We also assessed the clinical symptoms, physical examination findings, and laboratory data including the type of anti-ARS antibodies. For a further analysis, the data of patients were divided into two groups: the polymyositis (PM)/dermatomyositis (DM) group and the non-PM/DM group. *Results:* The ratio of men to women was almost 1:1. The median age at the time of the diagnosis was 53 years old. Anti-glycyl (anti-EJ) and anti-histidyl (anti-Jo-1) antibodies were more common than others. An analysis of the HRCT patterns of 23 ARS-ILD patients showed that the most common pattern was the nonspecific interstitial pneumonia (NSIP) pattern. The second most common pattern was the usual interstitial pneumonia (UIP) pattern. Between the PM/DM and non-PM/DM groups, no clear trends were noted in the age, sex ratio, proportion of HRCT patterns, or type of anti-ARS antibodies. *Conclusions:* This retrospective study demonstrated that ARS-ILD patients, regardless of myositis symptoms, most often showed the NSIP pattern on HRCT, as previously reported. However, unlike previous reports, the UIP pattern on HRCT was not rare.

**KEY WORDS:** ARS, HRCT, ASSD, UIP, NSIP, interstitial lung disease

### INTRODUCTION

Polymyositis (PM) and dermatomyositis (DM) are classified according to clinical features or myositis-specific autoantibodies (MSAs). The characteristics

of PM/DM-interstitial lung disease (ILD) differ according to MSAs (1). Among MSAs, anti-aminoacyl-tRNA synthetase (ARS) antibodies, which are particularly relevant to interstitial pneumonia, are enzymes that synthetase aminoacyl-tRNAs from specific amino acids and corresponding tRNAs. Eight different anti-ARS antibodies have been described: anti-threonyl (anti-PL-7), anti-alanyl (anti-PL-12), anti-isoleucyl (anti-OJ), anti-glycyl (anti-EJ), anti-asparaginy (anti-KS), anti-phenylalanyl (anti-ZO), anti-tyrosyl (anti-Ha), and anti-histidyl (anti-Jo-1) (2).

Among the clinical features of PM/DM, ILD is an especially important prognostic factor (3). The

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frequency of ILD in PM/DM is reported to be 30%–50%, although it has been suggested that the frequency may be slightly higher in Japan than elsewhere (4). In PM/DM-ILD, anti-ARS antibodies account for 40%–50% of all autoantibodies and are among the most frequent autoantibodies (4).

However, anti-ARS antibodies are closely associated with not only ILD but also arthritis, fever, Raynaud's phenomenon, and mechanic's hand, forming a form of the disease known as Antisynthetase syndrome (ASSD) (5, 6). Although there are differences in the prevalence of certain clinical findings among different ARS antibody groups, the presence of these antibodies does not have a substantial impact on the overall clinical presentation and survival of ASSD patients, indicating the syndrome's heterogeneity (7).

Among these clinical manifestations, ILD is especially frequent in ASSD, being reported in 70%–90% of cases (8, 9). In ASSD patients, ILD has been found to increase morbidity and mortality (6). Furthermore, myositis is not universal and can develop subsequent to the diagnosis of ASSD. Myositis is recognized to precede ILD in only 12.5% of ASSD patients, whereas ILD precedes myositis in 37.5% of these patients, and in 50% both occur simultaneously (10). Therefore, at the beginning of the clinical course, ASSD patients showing ILD may be diagnosed with idiopathic interstitial pneumonia (IIP). It has been reported that anti-ARS antibodies were detected in 7%–25% of patients diagnosed with IIPs (11, 12).

Anti-ARS antibodies are thus not rare among ILD patients. Furthermore, it has been suggested that they form a unique syndrome in ASSD, which is closely related to the development of ILD and correlated with the patient prognosis. Nevertheless, little research has been done on the high-resolution computed tomography (HRCT) findings in patients with anti-ARS antibody-positive ILD (ARS-ILD). Therefore, the present study clarified the HRCT findings of patients with ARS-ILD.

## PATIENTS AND METHODS

We reviewed the medical records of all Japanese patients admitted to the Department of Respiratory Medicine and Rheumatology, Tokushima University Hospital from October 2017 to March 2022. Among the 42 patients tested for anti-ARS antibodies,

the 24 who were positive for anti-ARS antibodies were enrolled in this study. Myositis-specific and myositis-associated autoantibodies (anti-Jo-1, anti-PL-7, anti-PL-12, anti-EJ, and anti-OJ) and anti-Ro-52 antibody were identified by a line immunoassay (Myositis Profile Euroline Blot test kit; Euroimmun, Lübeck, Germany).

We extracted and evaluated the following from the patients' medical records: clinical symptoms, physical examination, laboratory data, and HRCT findings at the time of the diagnosis of ILD. CT scan patterns were categorized as usual interstitial pneumonia (UIP), nonspecific interstitial pneumonia (NSIP), NSIP with organizing pneumonia (NSIP+OP), OP, and diffuse alveolar damage (DAD) according to the 2013 American Thoracic Society (ATS) / European Respiratory Society (ERS) classification of idiopathic interstitial pneumonia (13) by two pulmonologists and one expert thoracic radiologist. Patterns that could not be classified as those listed above were collectively considered an unclassifiable CT pattern. The images were randomized and reviewed independently by two pulmonologists and one expert thoracic radiologist. Discrepant interpretations were resolved by consensus through discussion.

For further analyses, the data of patients were divided into two groups: those who met the diagnostic criteria for PM or DM (14) and those who were not diagnosed with PM/DM.

The significance of differences between the groups was analyzed by a *t*-test and Fisher's exact test. *P* values of <0.05 were considered to be significant. Statistical analyses were performed using the GraphPad Prism software program Ver. 9.4.0 (GraphPad Software, La Jolla, California USA).

This study has been approved by the institutional review board of Tokushima University (Approval number: 2924).

## RESULTS

### *Clinical features*

Table 1 shows the clinical characteristics of patients enrolled in this study. The ratio of men to women was almost 1:1. The median age at the diagnosis was 53 (range 27–79) years old. Thirteen (54%) patients were current or past smokers. ILD was extremely frequent, occurring in 96% of all patients.

**Table 1.** Patient characteristics

	All patients	PM/DM group		non-PM/DM group	p-value
Total subjects, n (%)	24	13		11	
Female	12 (50)	6 (46)		6 (55)	>0.999
Age (years)					
Median	53	53		61	
Range	27-79	27-71		47-79	0.058*
Smoking history (current or past), n (%)	13 (54)	6 (46)		7 (64)	0.444
Clinical symptoms, n (%)					
Cough	11 (46)	4 (36)		7 (64)	0.217
Dyspnea	15 (63)	8 (62)		7 (64)	>0.999
Muscle weakness	13 (54)	13 (100)		0	<0.001
Mechanic's hand	9 (38)	5 (38)		4 (36)	>0.999
Fever	8 (33)	8 (62)		0	0.002
Arthritis	5 (21)	5 (38)		0	0.041
Raynaud's phenomenon	1 (4)	0		1 (9)	0.458
Interstitial lung disease	23 (96)	12 (92)		11 (100)	>0.999
Types of anti-ARS antibodies, n (%)					
EJ	8 (33)	3 (23)		5 (45)	0.390
Jo-1	4 (17)	3 (23)		1 (9)	0.596
PL-7	2 (8)	1 (8)		1 (9)	>0.999
PL-12	2 (8)	1 (8)		1 (9)	>0.999
EJ+PL-7	2 (8)	2 (15)		0	0.481
Jo-1+PL-12	1 (4)	1 (8)		0	>0.999
Other	5 (21)	2 (15)		3 (27)	0.629
Positive Anti-Ro-52 antibody, n (%)	20 (83)	13 (100)		7 (64)	0.031
Diagnosis, n		PM	6	IIPs	10
		DM	7	CHP	1

Abbreviations: PM, polymyositis; DM, dermatomyositis; ARS, aminoacyl-tRNA synthetase; IIPs, idiopathic interstitial pneumonias; CHP, chronic hypersensitivity pneumonitis. The association between the PM/DM and non-PM/DM groups was assessed using Fisher's exact test or a t-test (\*).

The pulmonary symptoms were cough (46%) and dyspnea (63%). The extra-pulmonary symptoms, in descending order of frequency, were muscle weakness (54%), mechanic's hands (38%), a fever (33%), arthritis (21%), and Raynaud's phenomenon (4%). Muscle weakness, a fever, and arthritis were only observed in the PM/DM group. In the non-PM-DM group, the most common extra-pulmonary symptom was mechanic's hand.

Overall, anti-EJ (33%) and anti-Jo-1 (17%) antibodies were more common than others, similar to when the analysis was limited to the PM/DM group. In contrast, in the non-PM/DM group, only anti-EJ

antibodies were more common than others. In the PM/DM group, both anti-EJ and anti-PL-7 antibodies or both anti-Jo-1 and anti-PL-12 antibodies were detected in three cases. Overall, there were five cases in which the type of ARS antibodies could not be identified with the test kit used in the present study. Anti-Ro-52 antibody was detected in 20 (83%) patients, more in the in the PM/DM group ( $p=0.031$ ).

The following disorders were definitively diagnosed: 13 patients with PM/DM, 10 patients with IIP, and 1 patient with chronic hypersensitivity pneumonitis (CHP).

Table 2 shows the results of laboratory examinations at the first visit. The serum creatinine kinase level was elevated in the PM/DM group, and the serum Krebs von den Lungen-6 (KL-6) levels were elevated in both groups.

### Chest radiographic findings

An analysis of the HRCT patterns at the time of diagnosis of the 23 ARS antibody-positive patients with ILD showed that the most common pattern was the NSIP pattern, which was observed in 12 patients (Table 3, Figure 1), followed by the UIP pattern, which was observed in 5 cases (Table 3, Figure 2). Clear trends were not observed in the age, sex ratio, proportion of PM/DM cases, or type of anti-ARS antibodies, even when classified by imaging pattern.

In previous reports (6, 15-20) that performed a similar analysis, the NSIP pattern was also the most common, similar to the present study (Table 4). However, the proportion of UIP patterns in this study was higher than in most previous reports. The proportions of IIP, PM/DM, and clinically amyopathic dermatomyositis (CADM) included differed among studies. Immunosuppressive therapy was generally chosen as the initial treatment in all cases, except those that showed a UIP pattern and were clinically diagnosed with IIP.

In a few cases, the subsequent imaging course could be followed up. In one of these cases, the HRCT images changed during the course of immunosuppressive therapy. HRCT of the lower lung zone of a 47-year-old man with anti-EJ antibody-positive disease initially showed a NSIP+OP CT

**Table 2.** Laboratory findings

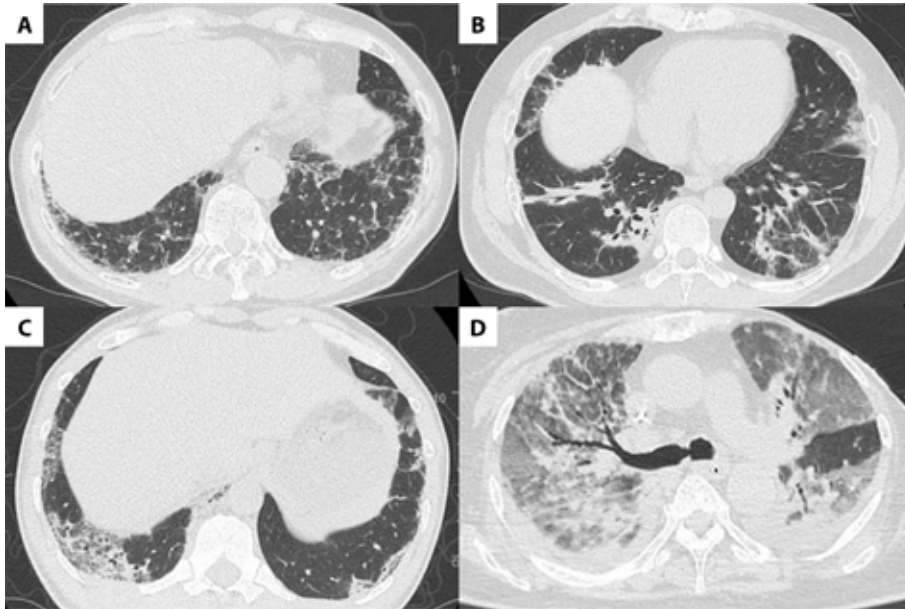
	All patients	PM/DM group	non-PM/DM group	<i>p</i> -value
	(n=22)	(n=11)	(n=11)	
WBC, / $\mu$ L	8700 (4000-24000)	10400 (4000-17000)	6700 (4300-24000)	0.401
CRP, mg/L	0.6 (0.0-9.8)	1.8 (0.1-7.4)	0.2 (0.0-9.8)	0.351
CK, U/L *	131 (34-11850)	2673.5 (86-11850)	66 (34-133)	0.017
	(n=20)	(n=10)	(n=10)	
ALD, U/L *	27.8 (8.3-261.1)	30.4 (8.5-261.1)	8.3	0.503
	(n=10)	(n=9)	(n=1)	
LDH, U/L	257 (134-1461)	392 (134-1461)	234 (161-513)	0.041
KL-6, U/mL	798.5 (133-6072)	708 (133-1846)	1174 (360-6072)	0.111
SP-D, ng/mL*	143 (39.3-669.0)	133 (39.3-501.0)	277 (84.4-669.0)	0.102
	(n=19)	(n=10)	(n=9)	

Data are presented as the median (range). \* Collected samples were limited. Abbreviations: PM: polymyositis; DM: dermatomyositis; WBC: white blood cell; CRP: C-reactive protein; CK: creatine kinase; ALD: aldolase; LDH: lactate dehydrogenase; KL-6: Krebs von den Lungen-6; SP-D: Surfactant Protein-D. The association between the PM/DM and non-PM/DM groups was assessed using a *t*-test.

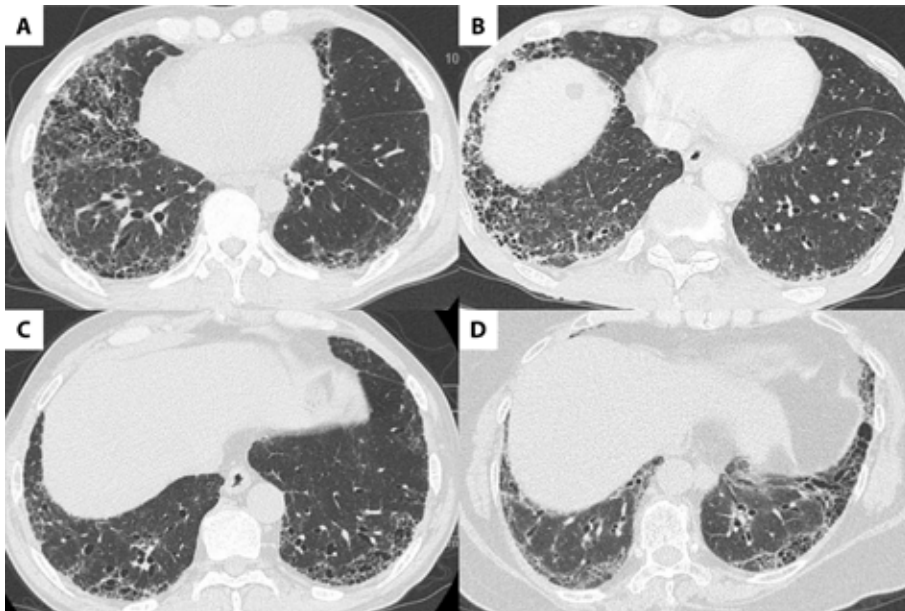
**Table 3.** HRCT patterns

HRCT pattern	Number of patients	Median age, years	Females, n (%)	PM/DM, n (%)	EJ, n (%)	Jo-1, n (%)	PL-7, n (%)	PL-12, n (%)
UIP	5	64	2 (40)	2 (40)	2 (40)	1 (20)	1 (20)	0
NSIP	12	54	7 (58)	7 (58)	6 (50)	1 (8)	2 (17)	3 (25)
NSIP+OP	3	47	1 (33)	1 (33)	1 (33)	2 (67)	0	0
OP	1	40	0	1 (100)	0	0	1 (100)	0
Other *	2	57.5	1 (50)	1 (50)	1 (50)	1 (50)	0	0

Abbreviations: HRCT: high-resolution computed tomography; UIP: usual interstitial pneumonia; NSIP: nonspecific interstitial pneumonia; OP: organizing pneumonia; PM: polymyositis; DM: dermatomyositis. \* HRCT patterns other than UIP, NSIP, NSIP+OP, OP.



**Figure 1.** Representative HRCT images of ARS-ILD showing HRCT patterns other than the UIP pattern. (A) HRCT images of a 69-year-old man positive for other anti-ARS antibody show the nonspecific interstitial pneumonia (NSIP) pattern. (B) HRCT images of a 47-year-old man positive for anti-EJ antibody show the NSIP with organizing pneumonia (NSIP+OP) pattern. (C) HRCT images of a 40-year-old man positive for anti-PL-7 antibody show the OP pattern. (D) HRCT images of a 79-year-old woman positive for anti-EJ antibody show the diffuse alveolar damage (DAD) pattern.

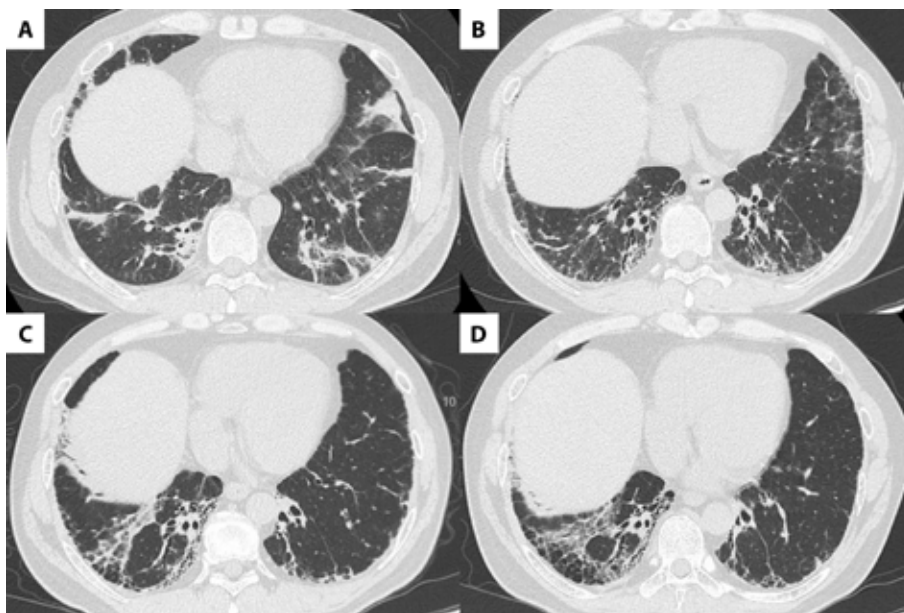


**Figure 2.** Representative HRCT images of ARS-ILD showing the UIP pattern. (A) High-resolution computed tomography (HRCT) images of a 56-year-old man positive for anti-Jo-1 antibody show the usual interstitial pneumonia (UIP) pattern. (B) HRCT images of a 69-year-old man positive for anti-EJ antibody and anti-PL-7 antibody show the UIP pattern. (C) HRCT images of a 64-year-old man positive for anti-EJ antibody show the UIP pattern. (D) HRCT images of a 66-year-old woman positive for other anti-ARS antibody show the UIP pattern.

**Table 4.** HRCT patterns, previous reports and the present study

	Year	Number Of patients	HRCT pattern					Diagnosis			
			UIP	NSIP	NSIP+OP	OP	Other*	Connection tissue disease			IIPs
								PM/DM	CADM	Other	
Wei Wu et al. <sup>15</sup>	2023	47	8.5%	38%	15%	30%	8.5%	N/A			
Elisa Baratella et al. <sup>16</sup>	2021	22	14%	36%	9%	23%	18%	N/A			
Hui Liu et al. <sup>17</sup>	2019	69	9%	64%	7%	19%	1%	N/A			
Yuko Waseda et al. <sup>18</sup>	2016	64	2%	55%	34%	6%	3%	55%	0%	9%	36%
Hironao Hozumi et al. <sup>19</sup>	2016	26	8%	50%	42%	0%	0%	58%	42%	0%	0%
Marie-Pierre Debray et al. <sup>20</sup>	2015	33	0%	45%	24%	21%	9%	N/A			
Marie Isabelle et al. <sup>6</sup>	2012	69	22%	59%		19%		100%			
The present study		23	22%	52%	13%	5%	8%	52%	0%	0%	43%

Abbreviations: HRCT: high-resolution computed tomography; UIP: usual interstitial pneumonia; NSIP: nonspecific interstitial pneumonia; OP: organizing pneumonia; PM: polymyositis; DM: dermatomyositis; CADM: clinically amyopathic dermatomyositis; IIPs: idiopathic interstitial pneumonias. \* HRCT patterns other than UIP, NSIP, NSIP+OP, OP.



**Figure 3.** Initial and follow-up HRCT images of a 47-year-old man with ARS-ILD. (A) High-resolution chest tomography (HRCT) images of lower-lung zones in a 47-year-old man positive for anti-EJ antibody show the nonspecific interstitial pneumonia-organizing pneumonia (NSIP-OP) CT pattern. (B) Same patient; 8 months after the start of immunosuppressive therapy. Consolidation has largely improved. (C) Same patient; 3 years after the start of treatment. The subpleural predominant reticular shadow has progressed. (D) Same patient; 5 years after the start of treatment. With the appearance of honeycombing, the HRCT findings changed to conform to the definite UIP pattern.

pattern (Figure 3A). Eight months after immunosuppressive therapy was started based on the diagnosis of IIP, however, the consolidation had largely improved, although reticular shadows with traction bronchiectasis remained (Figure 3B). After a further

two years, the subpleural predominant reticular shadow had progressed (Figure 3C). Five years after the start of treatment, with the appearance of honeycombing, the HRCT findings changed to conform to the definite UIP pattern (Figure 3D).

## DISCUSSION

In the present study, we assessed the characteristics, including HRCT patterns, of patients with ARS-ILD. Our findings showed that, similar to previous reports, anti-EJ and anti-Jo-1 antibodies were the common type of antibody (21), and the NSIP pattern was the most common HRCT pattern (6, 15-20). Surprisingly, however, a significant number of ARS-ILD patients in the present study showed the UIP pattern, which has been reported to be a poor prognostic factor for ARS-ILD on HRCT (17).

In the present study, the proportion of ARS-ILD cases showing the UIP pattern was almost equal between PM/DM and non-PM/DM (IIP). The analysis of HRCT patterns in ARS-ILD by Waseda et al. included the highest number of IIP cases reported to date (18). In that analysis, the proportion of diagnoses in the cases for which the HRCT pattern was reviewed was similar to that in the present study. However, the UIP pattern only accounted for 2% of the total in their study. Even in the analysis of HRCT patterns in ARS-ILD by Hozumi et al., which did not include any IIP cases, the UIP pattern accounted for only 8% of the total (19). In contrast, Isabelle et al. reported that the frequency of the UIP pattern was 33.3% and 17.6% in anti-PL7/PL12 antibody-positive and anti-Jo-1 antibody-positive ILD patients, respectively (6). Therefore, we suspect that there were other reasons for the difference in the proportion of UIP patterns aside from the difference in the proportion of PM/DM.

One possible reason for this may be the difference in the time period when HRCT patterns were examined, which is also mentioned by Waseda et al. as a limitation of their study (18). However, Debray et al. also reported that the UIP pattern was 0% at the time of their analysis, but honeycombing increased or appeared in 10 out of 26 (38%) of the patients during follow-up CT (20). They also found that honeycombing increased more frequently in the follow-up of patients with an increase in the overall disease extent than in those with a stable or decreased disease extent (20). As all of these previous studies were retrospective (6, 15-20), there were various time phases of HRCT at the time of the initial diagnosis. Similarly, in our study, we also found one case that was initially diagnosed as the NSIP pattern but later changed to the UIP pattern. It has been previously suggested that NSIP patterns can change

to UIP patterns as the disease progresses (22, 23). Wu et al. reported that among patients with an initial non-fibrotic pattern, the main CT abnormality disappeared in 23% of patients and progressed to a fibrotic pattern in more than half of the patients (15). In their analysis, the initial fibrotic pattern tended to persist, and ILD progression was associated with decreased survival (15). Taken together, these findings suggest that the differences in the time taken from the onset of ILD to the initial examination from other studies might have influenced the results.

In contrast to previous reports on HRCT patterns, histopathological reports on ARS-ILD indicate that the UIP pattern is observed as often as the NSIP pattern (24). Furthermore, it has also been indicated that the UIP pattern is the most common pattern in ILD patients with anti-Jo-1 antibodies, although the NSIP and OP patterns are also observed (24). However, another study reported that ARS-ILDs usually showed NSIP or OP patterns rather than UIP or DAD patterns (25). Watanabe et al. reported that the UIP pattern was observed in two of the eight ARS-ILD cases for which a pathological diagnosis was made (12). Thus, the frequency of pathological patterns in ARS-ILD varies among reports, but as with the examination of HRCT patterns, the UIP pattern does not appear to be very rare.

However, it has also been reported that cases of ARS-ILD histologically diagnosed with the UIP pattern differed from the typical histology of UIP in that there was moderate cellular infiltrate and lymphoid follicles but only temporal heterogeneity, microscopic honeycomb lung and subpleural dense fibrosis (12). These findings suggest that, unlike idiopathic pulmonary fibrosis (IPF), ARS-ILD showing the UIP pattern may benefit from immunosuppressive agents as well as antifibrotic drugs. Under the latest IPF guidelines, the diagnosis can be made without histological findings if HRCT shows a typical UIP pattern (26). However, these unique histological features of these UIP patterns in ARS-ILD suggest the importance of measuring anti-ARS antibodies and screening positive cases, even when patients do not present any symptoms of myositis and show a typical UIP pattern on HRCT.

Several limitations associated with the present study warrant mention. First, because this was a retrospective study, as in previous reports, there were various time phases for chest CT at the time of the initial examination. Second, the study may have

included selection bias, as not all patients with ILD who visited our institution were tested for anti-ARS antibodies; it was up to the attending physician to decide whether or not to test. Third, the sample size was small because of the single-center setting with the rare disease of ARS-ILD. Fourth, unknown and unidentified anti-ARS antibodies not distinguished by the line immunoassay used in this study might have affected the results. Given the above, a prospective study including more institution and more patients is needed to address these limitations.

This retrospective study demonstrated that ARS-ILD patients, regardless of myositis symptoms, most often showed the NSIP pattern on HRCT, as previously reported. However, unlike previous reports, ARS-ILDs showing a UIP pattern was not rare.

**Conflict of interest:** All authors declare that they have no conflict of interest. This research did not receive received specific funding from any public, commercial or non-profit funding bodies.

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