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Prognostic factors of interstitial lung disease progression at sequential HRCT in anti-synthetase syndrome

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Abstract

Objectives Interstitial lung disease (ILD) is a common extra-muscular manifestation of anti-synthetase syndrome (ASS) and the main cause of morbidity and mortality in patients with ASS. Data on prognostic factors in these patients are lacking.

Methods A total of 69 patients with ILD and positivity for at least one of the following autoantibodies were included: anti-Jo-1, anti-PL7, anti-PL12, and anti-EJ. Relevant clinical characteristics were registered. According to the changes in the extent of abnormalities at the follow-up on high-resolution computed tomography (HRCT), three groups were defined: the regression, stability, and deterioration groups. Univariate analysis was performed to evaluate possible prognostic factors and multivariate analysis by logistic regression was then applied to determine the independent prognostic factors in ASS-ILD.

Results The cohort comprised 69 patients positive for anti-synthetase antibodies, i.e., 30 for anti-Jo-1, 16 for anti-EJ, 13 for anti-PL7, and 10 for anti-PL12. The mean length of follow-up was 15 months. Sex, age at diagnosis, fever at presentation, and counts of $CD3^+CD4^+$ cells were significantly different among the three groups. According to the multivariate analysis, fever at presentation, lower counts of $CD3^+CD4^+$ cells, and a pattern of usual interstitial pneumonia were the three independent risk factors for poor outcomes of ASS-ILD.

Conclusions At the onset of ASS, some clinical features and HRCT pattern of ILD may suggest an unfavorable outcome of lung involvement on HRCT, even with routine therapy. These factors may contribute to the high long-term mortality of ASS.

Key Points

- *Evaluation of lung involvement on HRCT is important in the follow-up of patients with interstitial lung disease related to anti-synthetase syndrome (ASS-ILD).*
- *The interstitial lung disease related to ASS responds to the treatment variably.*
- *Some clinical and imaging characteristics are associated with poor prognosis in patients with ASS-ILD, including fever at diagnosis, a lower serum $CD3^+/CD4^+$ level, and a UIP pattern.*

Keywords Polymyositis · Dermatomyositis · Interstitial lung disease · Prognosis

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Abbreviations

AIP	Acute interstitial pneumonia pattern
ANA	Anti-nuclear antibody
ASS	Anti-synthetase syndrome
CI	Confidence interval
CK	Creatine kinase
CRP	C-reactive protein
CTDs	Connective tissue diseases
DLCO	Diffusion capacity of the lung for carbon monoxide
ESR	The erythrocyte sedimentation rate
FEV1	Forced expiratory volume
FVC	Forced vital capacity
GGO	Ground glass opacities
HRCT	High-resolution computed tomography

ILD	Interstitial lung disease
NSIP	Nonspecific interstitial pneumonia
OP	Organizing pneumonia
OR	Odds ratio
PFT	Pulmonary function test
RF	Rheumatoid factor
UIP	Usual interstitial pneumonia
VC	Vital capacity

Introduction

At the 2017 European League Against Rheumatism and the American College of Rheumatology Annual Meeting, antisynthetase syndrome (ASS) was categorized as a new entity, being separated from other myositides. It is characterized by serum antibodies to aminoacyl-tRNA synthetase (i.e., anti-tRNA synthetase antibodies (ASA)) and the presence of myositis, polyarthritis, and interstitial lung disease (ILD). ASA are a family of cytoplasmic enzymes that catalyze the formation of aminoacyl-tRNA from a specific amino acid and its cognate tRNA and play a crucial role in protein synthesis. Eight self-antibodies to ASA have been identified to date. Anti-Jo-1 (anti-histidyl) antibody, the first antibody to be discovered, is also the most common (15–20%) [1–3]. Other ASA include anti-PL7, anti-PL12, anti-EJ, anti-OJ, anti-KS, anti-Zo, and anti-YRS [3].

In patients with ASS, ILD frequently predominates at the time of presentation with a prevalence ranging from 63 to 100% [3–5]. ILD is a serious complication that contributes to high morbidity and mortality in patients with ASS [4, 6, 7]. The most common radiological and histological pattern is nonspecific interstitial pneumonia (NSIP) [3, 8]. The treatment of ASS-ILD is not standardized. Likewise, the reported prognosis, which is estimated on the basis of long-term survival and deterioration of pulmonary function test (PFT) results, varies considerably from resolution to fatal ILD. Some studies have suggested that patients with ASS with non-Jo-1 antibodies, particularly anti-PL7 and anti-PL12, have a poorer pulmonary outcome than patients positive for Jo-1 antibodies [2, 4, 7, 9]. Other risk factors for poor survival are mostly related to pulmonary involvement, including severe dyspnea and isolated ILD at diagnosis. In contrast, muscle weakness at diagnosis of ASS is associated with a better prognosis [4]. Considering the results of these studies, the severity of ASS-ILD and its response to therapy are the key factors in the treatment of ASS. Evaluation of lung involvement on HRCT gives the crucial information for the severity of ASS-ILD, which decides the clinical strategy. Therefore, we investigated the prognostic factors predictive of a poor outcome of ASS-ILD on HRCT in this study.

Methods

Study population

This retrospective single-center study was conducted at China-Japan Friendship Hospital (Beijing, China). Patients hospitalized from January 2009 to October 2018 were selected. ASS-ILD was diagnosed by a multiple disciplinary team, including an expert rheumatologist and two experienced radiologists specialized on chest CT. We adopted the criteria for ASS proposed by Solomon et al [10] in 2011. The proposed alternative, stricter criteria require two major or one major and two minor criteria in addition to the presence of an aminoacyl-tRNA synthetase autoantibody. The two major criteria are ILD not attributable to another cause and polymyositis or dermatomyositis according to the criteria established by Bohan and Peter [11, 12]. The three minor criteria are arthritis, Raynaud's phenomenon, and mechanic's hands. Patients with other identifiable causes of ILD, including medication-related lung injury and environmental and occupational exposure, were excluded. Patients with heart failure and infectious pneumonia at the initial diagnosis were also excluded.

The demographic data collected from the medical records included age at diagnosis, sex, smoking history, duration of onset, clinical features at presentation, complications, associated CTDs (connective tissue diseases), PFT and laboratory data at the time of presentation, ILD presentation at baseline and at serial follow-up, and prior treatment and outcome of ILD.

The study was approved by the ethical committee in our institution. Informed consent was waived because this was a retrospective study.

Clinical and laboratory data

We obtained all clinical data from the medical charts of the period from admission to initiation of treatment. All patients underwent a detailed medical history and physical examination. Blood tests included measurement of creatine kinase (CK), C-reactive protein (CRP), the erythrocyte sedimentation rate (ESR), rheumatoid factor (RF), and anti-nuclear antibody (ANA).

PFT data included vital capacity (VC), forced VC (FVC), forced expiratory volume in 1 s (FEV1), and carbon monoxide diffusion capacity (DLCO). Values are expressed as the percentage of predicted normal values. A restrictive ventilatory defect was defined by a total lung capacity of < 80% of predicted. An obstructive ventilatory defect was defined by an FEV1/FVC ratio of < 70%. Blood gas analysis results were also recorded.

High-resolution computed tomography

HRCT images of the lung (slice thickness of 1.0 or 1.5 mm) acquired at the initial ILD diagnosis and at the latest follow-up

were reviewed. The follow-up duration was at least 2 months for those alive, except one patient who died 1 month after the disease onset. HRCT examinations were obtained at full inspiration, with the patient lying supine. HRCT examinations were comprised of 1.0-mm-thick slices obtained on multidetector-row CT volumetrically and reconstructed with a high-spatial-frequency algorithm. While blinded to the patients' conditions, two radiologists with more than 5 years of experience independently evaluated the HRCT images, categorizing the HRCT findings according to the 2013 American Thoracic Society classification of idiopathic interstitial pneumonia [13, 14] and the recommendations of the Fleischner Society [15] as follows: (1) usual interstitial pneumonia (UIP) pattern characterized by bilateral subpleural reticulation and honeycombing with lower lobe predominance with minimal or nonexistent ground-glass opacities (GGO); (2) NSIP pattern characterized by patchy or diffuse GGO with associated reticular opacities; (3) organizing pneumonia (OP) pattern with peribronchial or subpleural consolidation or GGO without fibrosis; (4) NSIP/OP pattern with consolidations superimposed on a background of GGO, with or without reticulations or traction bronchiectasis; and (5) acute interstitial pneumonia pattern (AIP) characterized by rapidly progressive hypoxemia and bilateral patchy GGO on HRCT, often with consolidation of the dependent lung in the early stage and distortion of bronchovascular bundles and traction bronchiectasis in the later stage. Readers also analyzed the presence of pleural or pericardial effusion. Divergent conclusions were resolved by consensus between the two observers.

Outcome of ILD

The duration of follow-up was noted. The last HRCT which was available in our system was considered as the end point of follow-up in patients with multiple examinations. Follow-up CT findings were compared with the initial findings for the extent of the abnormalities. The ILD course was categorized as regression, stability, or deterioration by serial CT assessment according to the study radiologists' interpretation, using the method by Akira et al [16]. Deterioration and regression of the overall disease extent were respectively defined by an increase or decrease of at least 10% of the overall disease extent, whereas stability was defined by changes of less than 10% [16].

Study design

Clinical, laboratory, radiological, and outcome data of all patients at diagnosis of ILD were analyzed. Predictive factors for a poor outcome at the end of follow-up were determined by comparing the regression, stability, and deterioration groups. Surviving patients with a follow-up of less than 2 months were not included in this analysis.

Statistical analysis

Results are expressed as mean ± standard deviation or median (range), as appropriate. Differences in categorical data were compared using the chi-square test or Fisher's exact test. Differences in parametric data were tested with analysis of variance for normally distributed data and the Kruskal–Wallis test for non-normally distributed data. A p value of < 0.05 was regarded as significantly different. Logistic regression was used for multivariable analysis of prognostic factors, including all factors for which p was < 0.05. Results are presented as odds ratio (OR), ± 95% confidence interval (CI), and interquartile range (IQR). All statistical calculations were performed using SPSS 17.0 for Windows (SPSS Inc.).

Results

Population (Table 1)

Sixty-nine medical records were initially reviewed. There was a female predominance in this study (male/female, 13/56; about 1:4.3) with a mean age of 53 years at ASS diagnosis (range, 26–80 years). Six patients (9%) were current smokers or ex-smokers. Four malignancies were recorded, i.e., two patients with breast cancer, one patient with thyroid cancer, and one patient with cervical carcinoma. Three tumors were diagnosed 1 year after the ASS diagnosis and that in the patient with thyroid cancer was discovered at the time of ASS diagnosis. No patients were given any medicine that could damage the lungs (Table 1).

We recorded the initial manifestations of patients with ASS, such as arthralgia, myositis, skin abnormalities, dysphagia, or other symptoms. Myositis (45/69, 65%) was the most common manifestation, followed by skin abnormalities (38/69, 55%), arthralgia (33/69, 48%), and mechanic's hands (33/69, 48%). At the time of diagnosis of ILD, pulmonary symptoms were consistent with dyspnea on exertion ($n = 28$, 41%) and fever ($n = 25$, 36%). Inspiratory fine crackles on auscultation of the chest were heard in every patient, but no patient had clubbed fingers.

The most common type of ASA was anti-Jo-1 in 30 patients (44%), followed by anti-EJ in 16 patients (23%), anti-PL7 in 13 patients (19%), and anti-PL12 in 10 patients (15%). No significant differences of ASA types were found among the three groups with different outcomes ($F = 5.936$, $p = 0.434$, Table 2). Nine patients (13%) had overlap with other CTDs, i.e., seven with Sjögren's syndrome, one with systemic sclerosis, and one with both Sjögren's syndrome and scleroderma.

The serum CK level was abnormal in 36 patients (36/49, 74%); the median serum CK level was 220 IU/L (IQR 63–1259 IU/L). The CRP level was abnormal in 24 patients (27/

Table 1 Comparison of clinical characteristics at presentation among patients with interstitial lung disease associated with anti-synthetase syndrome

	Total	Regression ($n = 33$)	Stability ($n = 23$)	deterioration ($n = 13$)	p value
Female, *n* (%)	56	26 (79)	22 (96)	8 (62)	0.034
Age at diagnosis (years)	53.0 ± 13.0	51.9 ± 13.3	50.3 ± 11.5	60.5 ± 13.1	0.042
Overlap with other connective tissue diseases, *n* (%)	9	4 (12)	3 (10)	2 (20)	1.000
Smoking history, *n* (%)	6	2 (6)	0	4 (30)	–
Cancer, *n* (%)	4	1 (0)	2 (10)	1 (10)	–
Syndrome					
Fever, *n* (%)	18	8 (20)	7 (30)	3 (20)	0.003
Dyspnea on exertion, *n* (%)	28	16 (50)	7 (30)	5 (40)	0.394
Arthritis, *n* (%)	33	14 (40)	14 (60)	5 (40)	0.300
Myalgia, *n* (%)	31	14 (40)	11 (50)	6 (50)	0.265
Muscle weakness, *n* (%)	30	11 (30)	12 (50)	7 (50)	0.265
Mechanic's hand, *n* (%)	33	17 (50)	12 (50)	4 (30)	0.393
Skin involvement, *n* (%)	38	16 (50)	14 (60)	8 (60)	0.574
Raynaud's phenomenon, *n* (%)	5	2 (10)	2 (10)	1 (10)	1.000
Proximal dysphagia, *n* (%)	12	5 (20)	3 (10)	4 (30)	0.345

59, 46%), the ESR was abnormal in 34 patients (34/63, 54%), and counts of $CD3^+CD4^+$ cells were abnormal in 15 patients (15/54, 28%). The mean serum CRP level was 2.43 mg/dL, the mean ESR was 33 mm/h, and the mean counts of $CD3^+CD4^+$ cells were 607 cells/μL. Antibodies other than ASA were present in 43 patients (43/64, 67%) (Table 3).

ILD investigations at presentation

PFTs were performed in 48 cooperative patients at the time of diagnosis of ILD. Thirty-eight patients had a restrictive pattern, and two patients had an obstructive ventilatory defect. The mean VC was 70% predicted, mean FVC was 72%, mean FEV1% was 71%, and mean FEV1/FVC ratio was 80%. Forty-three patients completed the DLCO examination successfully and impaired carbon monoxide diffusing capacity was observed in 38 patients, with a median DLCO of 55% (range, 22–100% predicted). The mean pH was 7.44, and the mean PaO_2 was 83%. None of these factors were significantly different among the three groups.

Table 2 Comparison of ASA subtypes among patients with interstitial lung disease associated with anti-synthetase syndrome

	Total	Regression ($n = 33$)	Stability ($n = 23$)	Deterioration ($n = 13$)	
Jo-1	30	16	11	3	
EJ	16	6	6	4	
PL7	13	5	3	5	$F = 5.936$
PL12	10	6	3	1	$p = 0.434$

ASA, anti-tRNA synthetase antibodies; *Jo-1*, histidyl tRNA synthetase; *EJ*, glycyl tRNA synthetase; *PL7*, threonyl tRNA; *PL12*, alanyl tRNA synthetase

All patients' HRCT findings were reviewed (Table 4). An NSIP pattern was found in 44 patients (64%), OP in 13 (19%) (Fig. 1), UIP in 6 (9%), NSIP-OP in 5 (6%), and acute interstitial pneumonia in 1 (1%). HRCT showed pleural effusion in 5 patients, pericardial effusion in 6 patients, and combined pleural and pericardial effusion in 2 patients. None of these factors were significantly different among the three groups.

Treatment

Treatment information was available for all patients except one who accepted traditional Chinese medicine. Thirty-six patients were treated with combination therapy, and 32 received steroid monotherapy. The most commonly used combination therapy was prednisone and cyclophosphamide in 28 patients, followed by prednisone and mycophenolate mofetil in 3 patients, prednisone and methotrexate in 2 patients, prednisone and intravenous immunoglobulins in 1 patient, and prednisone and both cyclophosphamide and intravenous immunoglobulins in 1 patient. There was no statistically significant difference between steroid monotherapy and combined therapy in the three groups ($p = 0.942$).

Outcome of ILD

The median follow-up was 15 months (range, 2–96 months). The reviewers showed consistency in the evaluation of lesion changes in all cases except one with

Table 3 Comparison of serology features at presentation among patients with anti-synthetase syndrome associated with interstitial lung disease

	Total	Regression	Stability	Deterioration	*p* value
ANA (< 1:40), 1:*n* (%)	29/63 (46)	14/30 (50)	7/21 (30)	8/12 (70)	0.180
SSA, 1:*n* (%)	11/58 (19)	4/26 (20)	4/18 (20)	3/12 (30)	0.748
Ro-52, 1:*n* (%)	31/58 (53)	14/26 (50)	11/22 (50)	6/10 (60)	0.870
CRP (< 0.8 mg/dL) (*n*)	2.43 ± 4.56 (59)	1.61 ± 2.10 (29)	2.01 ± 3.82 (19)	5.29 ± 8.40 (11)	0.105
RF (< 20 IU/mL) *a* = < 20, 1:*n* (%)	13/53 (25)	6/26 (20)	4/17 (20)	3/10 (30)	0.916
ESR (0–20)[a]	33.03 ± 27.54	27.17 ± 22.56	36.45 ± 34.88	41.31 ± 24.13	0.245
$CD3^+/CD4^+$ cells (380–1208)[b]	607.15 ± 455.90	716.26 ± 517.63	571.28 ± 328.49	287.11 ± 182.32	0.040
CK (26–200)[c], median (IQR) years	231.00 (59.75–1356.75)	123.00 (49–819)	676.50 (61.25–1915.73)	280.50 (104.75–1526.25)	0.424

IQR, interquartile range; *ANA*, anti-nuclear antibody; *SSA*, anti-Sjögren's syndrome–related antigen; *CRP*, C-reactive protein; *RF*, rheumatoid factor; *ESR*, erythrocyte sedimentation rate; *CK*, creatine kinase

[a] In total, 55 patients were assessed (regression, $n = 30$; stability, $n = 20$; deterioration, $n = 13$)

[b] In total, 48 patients were assessed (regression, $n = 31$; stability, $n = 14$; deterioration, $n = 9$)

[c] In total, 45 patients were assessed (regression, $n = 23$; stability, $n = 16$; deterioration, $n = 10$)

different lung inflation between the two scans. The case was finally classified as no change by the calculation of lesion area to sectional area ratio on the post-processing workstation. Compared with the baseline CT findings, regression was observed in 33 patients (48%), the disease extent on HRCT remained stable in 23 patients (33%), and deterioration was observed in 13 patients (19%) on follow-up CT. Follow-up time in the regression, stability, and deterioration groups was 17.8 (S.D. 19.2), 12.7 (S.D. 10.1), and 16.8 (S.D. 14.1) months. One 48-year-old patient died of acute respiratory distress syndrome at 1 month of follow-up (Fig. 2). At the end of the follow-up period, there was no exacerbation of respiratory symptoms in the patients with regression or stability of disease extent on HRCT. Four patients relapsed one time in the course of treatment or after the initial treatment.

Table 4 Comparison of ILD pattern on HRCT at presentation among patients with interstitial lung disease associated with anti-synthetase syndrome

	Total	Regression ($n = 33$)	Stability ($n = 23$)	Deterioration ($n = 13$)	
NSIP	44	21	16	7	
OP	13	8	3	2	
NSIP-OP	5	3	1	1	
UIP	6	0	3	3	$F = 8.479$
AIP	1	1	0	0	$p = 0.159$
Pleural effusion	7	5	0	2	$p = 0.120$
Pericardial effusion	8	2	3	3	$p = 0.132$

NSIP, nonspecific interstitial pneumonia; *OP*, organizing pneumonia; *UIP*, usual interstitial pneumonia; *AIP*, acute interstitial pneumonia

Univariate analysis (summarized in tables)

The difference in sex ($F = 6.562$, $p = 0.034$) and age ($F = 4.295$, $p = 0.042$) among the three groups was statistically significant. An older age at diagnosis was apparent in patients with a poor prognosis (deterioration group vs. regression group, $p = 0.042$; deterioration group vs. stability group, $p = 0.023$).

Eight patients in the regression group, five in the stability group, and nine in the deterioration group had a fever at the time of diagnosis, with significant differences in frequency ($\chi^2 = 11.704$, $p = 0.003$). There is a significant difference of the $CD3^+CD4^+$ cell counts at diagnosis among the three groups ($F = 3.438$, $p = 0.040$).

However, neither the ASA types nor HRCT patterns showed significant differences among the three groups. Additionally, no differences were noted in therapy methods or PFT data.

Multivariable analysis

We chose the following possible significant factors for logistic regression to determine the independent predictive factors for the prognosis of lung involvement on HRCT: sex, age at diagnosis, fever at presentation, lower counts of $CD3^+CD4^+$ cells, various types of ASA, and different types of ILD HRCT patterns. Among these factors, fever at presentation ($p = 0.005$; OR, 12.273; 95% CI, 2.168 to 69.459), $CD3^+CD4^+$ cell counts ($p = 0.036$; OR, 0.997; 95% CI, 0.995 to 1.000), and different types of ILD were the three independent risk factors for the outcome of ILD on HRCT. Fever at presentation, lower $CD3^+CD4^+$ cell counts are associated with lung deterioration at the follow-up. Compared with UIP, NSIP ($p = 0.042$; OR, 0.083; 95% CI, 0.008 to 0.912) and NSIP-OP ($p = 0.042$; OR 0.016; 95% CI, 0.000 to 0.541) predicted better outcomes of ILD.

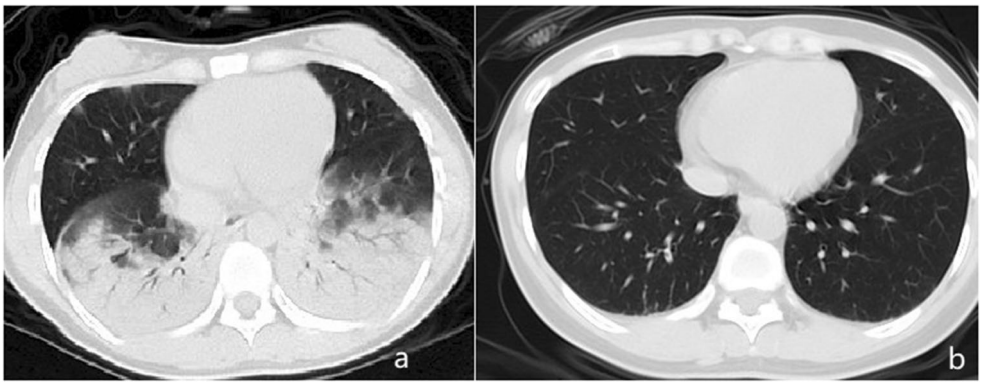

Fig. 1 **a** Axial computed tomography image of the lower lung zones in a 26-year-old woman with positive anti-Jo-1 antibody. It shows consolidations in a peribronchial distribution, consistent with an organizing pneumonia pattern. **b** Axial computed tomography image at the same level in the same patient 41 months later. After treatment with prednisolone and cyclophosphamide, the consolidations had completely resolved

Discussion

This study revealed the potential risk factors for the deterioration of lung involvement on HRCT, an indicator of ASS-ILD, in patients with ASS. We compared clinical, serological, and radiological aspects and various types of ASA in terms of the different outcomes of patients' lung disease. Furthermore, prognostic factors including fever at diagnosis, lower counts of $CD3^+CD4^+$ cells, and UIP pattern were found to predict the deterioration of ASS-ILD.

Our cohort was similar to prior ASS studies in terms of sex distribution and age at diagnosis [4, 17]. Our findings revealed that men and older age were associated with poorer outcomes of ILD, in accordance with previous studies [4, 18, 19]. In addition, fever and lower counts of $CD3^+CD4^+$ cells at diagnosis were positively associated with ILD deterioration in the univariate analysis and were also independent prognostic factors in the multivariable analysis. Fever and $CD3^+CD4^+$ cell counts are generally believed to reflect the inflammatory process. $CD3^+CD4^+$ cell counts are classified as T helper lymphocytes, which play an important role in inflammatory disease [20, 21]. Their decrease in patients with ILD suggests more unbalanced immunological reaction and the disease may even be more refractory to therapy. Our study further revealed that lower counts of $CD3^+CD4^+$ cells at diagnosis was associated with a poor outcome on HRCT, consistent with the findings of Marie et al [17].

Several other CTD-associated antibodies can be detected in patients with ASS. Previous series reported that 5% to 8% of cases of ASS manifest as overlapping syndromes with other CTDs including rheumatoid arthritis, lupus, scleroderma, and Sjögren's syndrome [1, 7, 22]. Anti-SSA antibodies, particularly anti-Ro52, occur in more than 50% of patients with ASS [23]. Some reports have highlighted that patients with ASS who are positive for anti-Jo-1 and anti-SSA/Ro antibodies have more severe ILD and a decreased response to treatment [24]. Our data suggested that 11.5% of patients with ASS had overlapping syndromes with other CTDs, although no effect on the outcome of

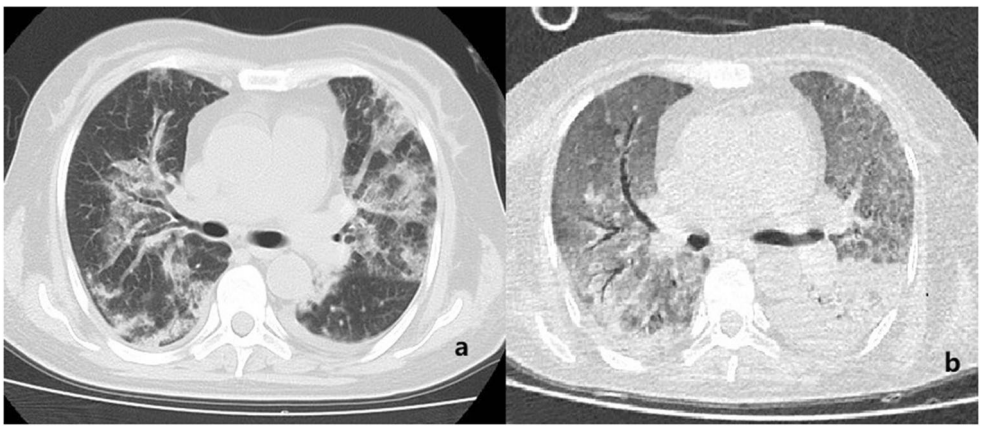

Fig. 2 **a** Axial computed tomography image of the middle lung zones in a 48-year-old woman positive for anti-PL7 antibody. It shows ground-glass opacity and consolidations in a peribronchial distribution, consistent with an organizing pneumonia pattern. **b** Axial computed tomography image at the same level in the same patient 1 month later shows extensive ground-glass opacity and consolidations in the left lower lung. Despite combination treatment, the patient developed acute respiratory distress syndrome and died 3 days after the computed tomography examination

ILD was detected. Whether the coexistence of an anti-SSA/Ro-52 subset of antibodies and ASA leads to more severe lung disease remains to be further studied.

The HRCT pattern was identified as a predictive factor for an unfavorable lung condition. NSIP was the most common pattern at HRCT examinations, followed by OP and UIP [3, 8]. During the follow-up, most patients with NSIP remained stable or showed regression, while half of the patients with UIP deteriorated. Honeycombing, as the main finding of UIP, represents pulmonary fibrosis that is unresponsive to steroid and immunosuppressive therapy [17, 25]. In contrast, consolidation in OP and NSIP/OP is sensitive to steroid therapy, resulting in the regression of lung involvement (Fig. 1). Debray et al [25] reported that consolidations were resolved in 10 of 12 patients (83.0%) and that most patients (7/12, 58.3%) who initially had an OP or NSIP-OP pattern showed resolution or improvement, in accordance with the present study. Hence, UIP may be associated with poorer outcomes than NSIP/OP in patients with ASS patients.

In addition to the pattern of ILD, some previous studies suggested that certain ASA may be associated with certain ASS phenotypes, including the incidence and severity of lung involvement. With respect to the association between ASA and prognosis, previous reports have shown that various types of ASA predict variable outcomes [2, 3, 9, 26]. ILD is the most common cause of death, followed by malignancy, infection, and cardiovascular disease [27]. Anti-PL7 and anti-PL12 positivity are reportedly associated with a high burden of ILD [9]. In another study, ILD severity was associated with a worse prognosis for both anti-PL-7 and anti-PL-12 antibodies [4]. The survival rates of patients with anti-PL7 antibodies decreased more rapidly in the early than in the late stage during the long-term follow-up [4]. Anti-EJ-positive patients had better long-term outcomes than other patients with ASS. In our study, we found no associations between the subtype of ASA and ILD outcomes in both the univariate analysis and the multivariable analysis. This result seems to be different from most of the previous studies [2, 4, 9, 19, 28, 29]. However, because the presence of ILD is the factor associated with increased mortality and morbidity in patients with ASS-ILD, it is argued that the pulmonary involvement, not the subtype of ASA, is the factor associated with excess mortality. In a prospective 7-year study of 162 patients with idiopathic inflammatory muscle disease, Love et al [7] found 47 cases of ASS. The poor prognosis of ASS seems related not to the subtype of ASA but to the high rate of occurrence, severity, and frequent steroid resistance of ILD. In our opinion, this viewpoint may be rational. Because of the retrospective nature of our study, larger prospective studies are required to rigorously evaluate the possible association of ASA subtypes with the outcome of ASS-ILD.

One patient died of rapidly progressive ILD in our study. This female patient had anti-PL7 ASA and presented with dyspnea and muscle weakness. An OP pattern was found on her initial HRCT (Fig. 2). The disease deteriorated rapidly, and rapidly progressive ILD soon developed with resistance to prednisone and cyclophosphamide. The patient died 1 month after the onset. Previous studies have shown that such patients usually present with amyopathic ASS, even showing improvement in the initial phase and then develop progressive ILD [30]. Patients with an acute diagnosis frequently present with severe dyspnea associated with fever and usually corresponding to diffuse alveolar damage [30, 31]. As has been previously reported, rapidly progressive ILD does not respond to steroid and immunosuppressive therapy and contributes to the increased mortality rates of ASS [3].

This study has several limitations. First, only a small number of patients with non-anti-Jo-1 antibodies were included in the study, which limited the analysis of confounding factors. Second, PFT data at follow-up and histological evidence were not provided. PFTs may not reveal significant changes during a relatively short follow-up duration and the results are vulnerable to the noncooperation of the patients. Conversely, HRCT may demonstrate whether an appreciable response to therapy has occurred. From this viewpoint, HRCT is more suitable than PFT in the evaluation of ILD. Histological examination is useful for the differentiation of fibrotic NSIP and UIP. There is a possibility of underestimation of UIP in our study because histological results were not obtained. Third, the duration of follow-up may be not long enough for some patients. Those with a favorable response to therapy had a follow-up duration of only a few months, while those who showed unresponsiveness spent more time to confirm their worsening outcome. Information regarding relapse, which could indicate an unfavorable outcome, was not included in the analysis because of the relatively small numbers.

Conclusion

Our study has shown that men, the presence of older age, fever, and lower counts of $CD3^+CD4^+$ cells at initial diagnosis are more frequently associated with a poor outcome on HRCT in patients with ASS-ILD. Fever at diagnosis, lower counts of $CD3^+CD4^+$ cells and a UIP pattern may predict unfavorable lung deterioration on CT in patients with ASS-ILD. Knowledge of the predictors of ASS-ILD may be crucial to improve management in the early stage of the disease. However, further prospective series are required to better define the risk factors for ILD deterioration in the long term.

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Compliance with ethical standards

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Conflict of interest The authors declare that they have no conflict of interests.

Statistics and biometry No complex statistical methods were necessary for this paper.

Informed consent Informed consent was waived because this was a retrospective study.

Ethical approval The study was approved by the ethical committee in our institution.

Study subjects or cohorts overlap This study subjects or cohorts was original research that has not been published previously, and not under consideration for publication elsewhere.

Methodology
- Retrospective
- Diagnostic or prognostic study
- Performed at one institution

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