Clinical Features of Anti-Synthetase Syndrome Associated Interstitial Lung Disease: A Retrospective Cohort in China

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Abstract

Background

Antisynthetase Syndrome (ASSD) is a chronic autoimmune condition characterized by antibodies directed against an aminoacyl transfer RNA synthetase (ARS) along with a group of clinical features including the classical clinical triad: inflammatory myopathy, arthritis, interstitial lung disease (ILD). ASSD is highly heterogeneous due to the different organs involvement, and ILD is the main cause of mortality and function loss, which presents as different patterns when diagnosed. We designed this retrospective cohort to describe the clinical features and disease behavior of the ASSD associated ILD.

Methods

Retrospectively collected the data of 108 cases of ASSD associated ILD in Beijing Chaoyang Hospital since 2017.12 to 2019.3. Data was obtained from the Electronic Medical Record (EMR) system. Patients were divided into 5 groups according to the distinct Aminoacyl tRNA synthetases (ARS) antibodies.

Results

108 consecutive patients were recruited. 33 were with JO-1 positive and 30 were with PL-7 positive. 23 with EJ positive, 13 with PL12 positive and 9 with OJ positive. JO-1 group had a significant higher rate of mechanic's hand (57.6%) than other 4 groups. Polymyositis/ Dermatomyositis (PM/DM) was diagnosed in 25 (23.1%) patients and no difference was observed among the 5 groups. The anti-PL7 positive group had a higher frequency of UIP pattern (13.3%) than other 4 groups but the difference was not significant, and EJ group had the most frequent OP pattern (78.2%), which was significantly higher than PL-7 group ($P<0.001$) and PL-12 group ($P=0.025$).

The median follow-up time were 10.7 months. All received prednisone treatment, with or without immunosuppressants, and at the 6-month-follow up, the JO-1 group and EJ group had a significantly higher improvement of forced vital capacity than the other 3 groups ($P<0.05$), and PL-7 group had the lowest FVC improvement ($P<0.05$). The anti-Jo1-positive group and anti-EJ-positive group had significantly higher anti-RO52-positive occurrence than other 3 groups ($P<0.05$).

Conclusion

Anti PL-7 antibody had the same frequency as anti-JO1 in ASSD-ILD, in which the ILD pattern was different with distinct anti-ARS antibodies. All ASSD-ILD responded to therapy of steroids, with or without immunosuppressants. PL-7 group had a highest occurrence of UIP pattern, and significantly lower response to therapy.

Background

Antisynthetase Syndrome (ASSD) is a chronic autoimmune condition characterized by antibodies directed against an aminoacyl transfer RNA synthetase (ARS) along with a group of clinical features including the classical clinical triad: inflammatory myopathy, arthritis, interstitial lung disease(ILD), and the less common observed ones defined as “accompanying findings”, which are Raynaud’s phenomenon, Mechanic’s hands, fever. ASSD is heterogenous due to the different organs involved, the different onset timing of the triad, and the different response to steroids and immunosuppressive agents. There is no uniform criteria for the definition of ASSD, both Connor’s criteria (1) and Solomon’s Criteria(2) are used in different cohorts, and the latter was based on the presence of myositis. However, as a major form of organ involvement in ASSD, ILD is responsible for the severity of ASSD, and is a main cause of function loss and morbidity in different studies, no matter what criteria of ASSD was used(3, 4). Myositis, as one of the classic triad, might be absent at the time of ASSD diagnosis of ASSD yet occurred during follow up, and if a triad finding appeared more than three months after the previous one, it was defined as an “ex-novo” finding(5).

We designed this retrospective cohort study to learn the disease behavior of ASSD associated ILD, the subtype of ASSD-ILD, the response to medication of distinct (ARS), using Connor’s criteria on ASSD which published on *Chest* in 2010(1).

Materials And Methods

Patients. We retrospectively recruited patients with a diagnosis of ASSD who were referred to the Department Respiratory and Critical Care Medicine of the Beijing Chaoyang Hospital from 2017.12 to 2019.3. All patients’ data were used anonymously. Informed consents were waived for this study was retrospective and observational.

Data Acquisition. Data were obtained from the EMR. Patients recruited in this cohort had full data of blood test, chest HRCT scan and PFT before treatment, and a biopsy via bronchoscopy (transbronchial lung biopsy or transbronchial cryobiopsy) would be performed if it’s decided by the MDT discussion, which was composed of 2 pulmonologists, 1 rheumatologist, 2 radiologists, 1 pathologists, 1 physician of Occupational Medicine, and held routinely every week. All the patients in this cohort had full data of at least one follow-up 6 months after diagnosis, when CT scan and PFT were applied to evaluated the effectiveness of treatment. Patients with a rapidly progressed ILD were excluded because the PFT could not be performed(6). Patients with other connective tissue diseases including Rheumatoid Arthritis (RA), Systemic Sclerosis (SSc), Systemic Lupus Erythematosus (SLE), Sjögren Syndrome (SS), were excluded. Patients of Age < 18 years old or > 80 years old, or with a history of malignancy were excluded. A response to therapy was defined as an improvement of FVC of %predicted value, or a same FVC of predicted value with an improvement of respiratory symptoms, including cough and dyspnea.

Diagnostic Criteria. Diagnosis of ASSD was based on criteria proposed by Connor(1), et al, which is a positive serologic testing for an anti-ARS autoantibody(Jo-1, PL-7, PL-12, EJ, OJ), plus one or more of the following conditions: ☐Evidence of myositis by Bohan and Peter criteria, ☐Evidence of ILD, ☐Evidence of

arthritis by clinical examination, radiographic findings, or patient self-report, Unexplained, persistent fever, Raynaud phenomenon, Mechanic’s hand. The presence of ILD was evaluated by computed tomography (CT) and a MDT discussion. Radiological and pathological patterns of the ILD were classified as usual interstitial pneumonia (UIP), nonspecific interstitial pneumonia (NSIP), and organizing pneumonia (OP) by the MDT routinely held every week. RP-ILD (Rapidly Progressed ILD) was defined as a worsening of radiologic interstitial changes with progressive dyspnea and hypoxemia within 3 months after the onset of respiratory symptoms(6).

Anti-ARS antibodies analysis. The anti-ARS antibodies were identified using EUROIMMUN immunoblot according to the manufacturer’s instructions, including the anti-Jo1, anti-PL7, anti-PL12, anti-EJ, and anti-OJ antibodies. The results were considered positive if the bands showed moderate or strong reaction.

Statistical analysis. Statistical analysis was performed using SPSS software version 21.0. Chi-square and Fisher’s exact tests were used to compare the frequencies of the anti-ARS antibodies subgroups, the ILD pattern, the pulmonary function improvement, and the anti-Ro52 positive rate.

Result

Since December 2017 to March 2019, 827 patients with ILD were screened in the study, 115 were with positive ARS antibodies, and 7 with a rapidly progressed ILD were excluded, who were too weak to receive a PFT evaluation. Patients were divided into 5 groups according to the different ARS antibodies. All patients received treatment, with a base of prednisone of 0.5-1mg/kg/d, with or without an immunosuppressive agent, including cyclophosphamide (48 cases), Mycophenolate Mofetil (25 cases), and Tacrolimus (11 cases). 9 patients could not tolerate cyclophosphamide and were switched to Mycophenolate Mofetil (3 cases) and Tacrolimus (4 cases), 2 had cyclophosphamide cessation and maintained monotherapy of prednisone.

Demographic features: Tabel-1 showed the general clinical characteristics of the 108 ILD with different positive anti-ARS antibodies. The median follow-up time were 10.7 months. The mean age was 56.8±10.5 years. 2/3 of patients were female (M:F=36:72). No differences were observed between the demographic features of the 5 groups.

Frequency of distinct ARS. Of 108 cases with a ILD and a positive ARS, 33 (30.6%) were with anti-Jo1-positive, 30 (27.8%) were with anti-PL7-positive, 23 (21.3%) were with anti-EJ-positive, 12 (11.1%) were with anti-PL12-positive, 9 (8.3%) were with anti-OJ-positive. Seen in Table-1.

Table-1 Demographic Features

	Overall n=108	Jo1(+) n=33	PL7(+) n=30	EJ(+) n=23	PL12(+) n=13	OJ(+) n=9	P
Age	56.8±10.5	55.0±11.4	58.3±10.6	57.0±9.1	57.5±12.3	56.7±8.5	0.794
Female	72(66.1)	26(78.8)	18(60)	15(65.2)	7(53.8)	6(66.7)	0.217
Mechanic's hands	27(25)	18(54.5)	2(6.7)	4(17.4)	2(15.4)	1(11.1)	0.002
Clinical Features							
Skin Involvement (Gottron Papules/ Heliotrope rash)	38(35.0)	19(57.6)	5(16.7)	9(39.1)	2(15.4)	3(33.3)	0.054
PM/DM	25(23.1)	9(27.3)	6(20)	5(21.7)	3(23.1)	2(22.2)	0.725
Anti-Ro52	73(67.6)	29(87.9)	19(63.3)	21(91.3)	3(23.1)	1(11.1)	<0.001
ILD pattern (Radiological and Pathological diagnosis by MDT)							
OP	53	18	8	18	4	5	
NSIP	42	13	15	4	8	2	
OP+NSIP	9	2	3	1	1	2	
UIP	4	0	4	0	0	0	
Positive Anti-Ro52 antibody	73(67.6)	29(87.9)	19(63.3)	21(91.3)	3(23.1)	1(11.1)	

Comparisons of clinical characteristics. Of the 108 cases of ASSD-ILD, mechanic's hands were found in 27(25%) patients, and the anti-Jo-1 positive group had a significantly higher occurrence of mechanic's hand (57.6%) than the other 4 groups (P=0.002). Skin involvement (Gottron Papules and/or Heliotrope rash) was found in 38 (35.0%) patients, no differences were observed among the 5 groups (P=0.054). Polymyositis/Dermatomyositis (PM/DM) was diagnosed in 25 (23.1%) patients when time of ASSD diagnosis, according to the Bohan and Peter criteria(7, 8), and no difference of the occurrence was observed among the 5 groups (P=0.725). 2 patients were newly diagnosed dermatomyositis 10 months after the diagnosis of ASSD, when they complained about fever and myalgia during follow up, and when the prednisone had been tapered down to 10 mg qd, and both of them were in Jo-1 positive group, which could be considered as an "ex-novo" finding(5). Seen in Table 1.

Comparison of the ILD pattern. Of the 108 patients with ASSD-ILD, 30 cases received bronchoscopy for a transbronchial lung biopsy, 3 had bronchoscopy for a transbronchial cryobiopsy, to make a pathological diagnosis, and the radiological and pathological pattern of the ILD was discussed by the MDT. 53 were with an OP pattern(Fig1-2), 42 were with an NSIP pattern(Fig3-4), and 9 were with an OP+NSIP pattern, 4 were with a UIP pattern. All the 4 UIP patients were in PL7 group, which had a higher rate of UIP pattern than other 4 groups, but no significant difference was observed as a result of the small sample size. The anti-EJ-positive group had a highest frequency of OP pattern (78.3%), which was significantly higher than PL-7 group ($P<0.001$) and PL-12 group ($P=0.025$). The anti-JO1 group had a higher occurrence of OP pattern than the PL-7 group ($P=0.019$). Seen in Table-1 and Table-2.

Table-2 Comparison of the OP pattern

	EJ(+)	Jo1(+)	PL7(+)	PL12(+)	OJ(+)
	n=23	n=33	n=30	n=13	n=9
Jo1(+)	0.068	—	—	—	—
PL7(+)	0.001	0.019	—	—	—
PL12(+)	0.025	0.208	0.909	—	—
OJ(+)	0.397	1.000	0.203	0.567	—

Comparison of the PFT improvement. All the patients were treated with prednisone of 0.5-1mg/kg/day as an initial dose, with or without immunosuppressive agents, Each patient had at least one follow-up 6 months after diagnosis. The PFT (FVC, DLCO) improvement of the 6-month follow-up were recorded (Table-3). A response to therapy was defined as an improvement of FVC of %predicted value, or a same FVC of predicted value with an improvement of respiratory symptoms, including cough and dyspnea .

Table-3 Improvement of PFT

Improvement of PFT (mean $\pm$ Std)	Jo1(+)	PL7(+)	EJ(+)	PL12(+)	OJ(+)
	n=33	n=30	n=23	n=13	n=9
Change of FVC % predicted value (%)	8.6 $\pm$ 4.4	1.1 $\pm$ 0.7	5.5 $\pm$ 3.8	2.3 $\pm$ 1.8	2.7 $\pm$ 1.6
Chang of DLCO% predicted value (%)	16.9 $\pm$ 9.8	9.1 $\pm$ 4.5	10.5 $\pm$ 5.4	10.0 $\pm$ 4.9	10.3 $\pm$ 4.8

The improvement of FVC: At 6 months follow up, the anti-JO1-positive group had a significantly higher FVC improvement than anti-PL7-positive group ($P<0.001$), than anti-PL-12-positive group ($P<0.001$), than anti-OJ-positive group ($P=0.004$), the anti-EJ-positive-group had a significantly higher FVC improvement than anti-PL7-positive group ($P<0.001$), than anti-PL12-positive group ($P=0.001$), than anti-OJ-positive group ($P=0.005$). The anti-PL7-positive group had the lowest FVC improvement among all groups, and it was significantly lower than the anti-PL12-positive group ($P=0.008$), than the anti-OJ-positive group ($P=0.006$), than anti-EJ-positive group and anti-JO1-positive group as described before. The FVC improvement between anti-OJ-positive and anti-PL12-positive group was not significant ($P=0.527$). The FVC improvement between anti-JO1-positive and anti-EJ-positive group was not significant ($P=0.966$). Seen in Table-4.

Table-4 Comparison of the FVC improvement

Improvement of FVC % predicted value (%)	EJ(+) (5.5±3.8)	JO1(+) (8.6±4.4)	PL7(+) (1.1±0.7)	PL12(+) (2.3±1.8)	OJ(+) (2.7±1.6)
JO1(+)	0.966	—	—	—	—
PL7(+)	0.001	0.001	—	—	—
PL12(+)	0.001	0.001	0.008	—	—
OJ(+)	0.005	0.004	0.006	0.527	—

The improvement of DLCO: The anti-JO1-positive group had the significantly higher improvement of DLCO than the anti-PL7-positive group ($P=0.011$), the anti-EJ-positive ($P=0.008$), the anti-PL12-positive group ($P=0.023$), respectively. The DLCO improvement of the other between-group differences were not significant ($P>0.05$). Seen in Table-5.

Table-5 Comparison of the DLCO improvement

Improvement of DLCO % predicted value (%)	EJ(+) (10.5±5.4)	JO1(+) (16.9±9.8)	PL7(+) (9.1±4.5)	PL12(+) (10.0±4.9)	OJ(+) (10.3±4.8)
JO1(+)	0.008	—	—	—	—
PL7(+)	0.432	0.011	—	—	—
PL12(+)	0.783	0.023	0.312	—	—
OJ(+)	0.907	0.063	0.455	0.903	—

Comparison of the myositis-associated antibodies. Anti-Ro52 antibodies was found positive in 73 (67.6%) cases, and anti-Jo1-positive group and anti-EJ-positive group had significantly higher anti-Ro52-positive rate than other 3 groups ($P<0.05$). Seen in Table-6.

Table-6 Comparison of the Anti-Ro52 antibody

Positive Anti-Ro52 antibody	EJ(+) (91.3%)	JO1(+) (87.9%)	PL7(+) (63.3%)	PL12(+) (23.1%)	OJ(+) (11.1%)
JO1(+)	1.000	—	—	—	—
PL7(+)	0.019	0.022	—	—	—
PL12(+)	0.001	0.001	0.015	—	—
OJ(+)	0.001	0.001	0.018	0.878	—

Discussion

In this study we compared the clinical features and disease behaviors of ASSD-ILD patients with different ARS. ASSD was first defined by Marguerie(9) as a relatively homogeneous syndrome comprising inflammatory myopathy, pulmonary fibrosis, arthritis in 1990 in a retrospective cohort of 29 patients, with 19 anti-JO1 positive, 4 anti-PL7 positive, and 6 anti-PL12 positive. JO1 is the most frequent antibody in all the ASSD studies and represents the most common form(10). Studies showed that specific ARS had different ASSD phenotype, such as skin involvement (heliotrope rash) was more frequent in anti-PL7-positive patients(3, 11), however, few research was performed to understand the correlation between different ARS antibodies and the ILD pattern, which is a common manifestation of ASSD and a main cause of death.

35-45% of patients diagnosed with PM/DM will be afflicted with ILD during the course of myositis(1), some reported the ILD prevalence of 65% in PM/DM(12). ILD occurs after the diagnosis of PM/DM in up to 40% of patients, and precedes the diagnosis of PM/DM in 20–30% of cases(13, 14), causing morbidity and mortality. OP, NSIP, mixed NSIP-organizing pneumonia pattern are more frequent than UIP pattern in PM/DM-ILD(12). The ARS antibodies, one of the myositis specific antibodies (MSA), are positive in 30-45% of patients with a myopathic inflammatory disease (3, 15), PM/DM patients with positive ARS had higher prevalence of ILD than those without such antibodies. ARS can also be positive in ILD patients who don't meet criteria of inflammatory myositis of any other CTDs, who were considered as idiopathic interstitial pneumonitis (IIP) with positive ARS antibodies, or could be classified as interstitial pneumonia with autoimmune features (IPAF) since 2015(16). ASSD is a term with more preference focusing on the ARS antibody, however, to date, there are no uniform diagnostic criteria of ASSD. In some cohorts the ASSD was defined with a presence of myositis(3), while Connor proposed his ASSD criteria in 2010, which is more pragmatic, defined by a positive ARS antibody plus one or more of myositis, ILD, arthritis, fever, Raynaud, Mechanic's hands(1). In patients with ASSD, the classic clinical triad (myositis, ILD,

arthritis) might have different time onset. In the large cohort of 828 ASSD patients (AENEAS collaborative group)(5), the onset mainly began with a single triad findings, and some cases presented as one/two triad findings in the clinical time course (5), just similar to our study.

ARS is a group of antibodies targeting at the ribonucleoproteins involved in protein synthesis, and eight anti-ARS Abs have been described: anti-histidyl (anti-JO1), anti-threonyl (anti-PL7), anti-alanyl (anti-PL12), antiglycyl (anti-EJ), anti-isoleucyl (anti-OJ), anti-asparaginyl (anti-KS), anti-phenylalanyl (anti-Zo), and anti-tyrosyl (anti-Ha) tRNAs, the former 5 of which are tested routinely in clinical practice.

Studies were applied to explore the significance of distinct ARS antibodies and results were different. JO1 is the most prevalent antibody in either ASSD (60-75%)(17, 18) or inflammatory myositis(found positive in 20-30% PM patients and in 5-10% DM patients)(2, 17). A cross-sectional and longitudinal analysis in 77 patients with inflammatory myositis associated ILD showed that the anti-JO1 positive patients(28) had worse lung function and CT scores over time compared to those without detectable ARS antibodies(19). While another retrospective study of 202 cases of ASSD showed that the 5- and 10-year unadjusted cumulative survival was 90% and 70% for anti-Jo1 positive patients respectively, which were significant better than that of non-JO1 patients ($P<0.005$)(18). However, in this cohort, the most common cause of death was pulmonary fibrosis (49%), which was similar between Jo-1 and non-JO1 patients ($P=0.511$)(18). In another cohort of 43 patients with ASSD associated ILD, 6 (14%) patients had died at 5 years, and the anti-JO1 positive ratio was significantly higher in the survivors (86 %) than that of the deceased patients (50 %) ,who had a significantly lower baseline FVC(20).

Anti-PL7/PL12 positive in ASSD patients were found to be associated with more aggressive ILD and decreased survival as compared with those with anti-JO1 antibody. An ASSD cohort included 75 JO1-positive cases, 15 PL7-positive cases, and 5 PL12-positive cases, and the anti-PL7/PL12 positive patients had more ILD compared with those with anti-Jo1 antibody (90% vs. 68%); anti-Jo1 antibody results in more severe myositis, joint impairment and increased risk of cancer(21). In a cohort of 7cases of anti-PL7 positive ASSD-ILD, lung biopsy revealed 50% cases of UIP(22).In another retrospective study of 20 cases of anti-JO1 positive ASSD-ILD, 35% of cases were with UIP pattern on lung biopsy(23). In a cohort of 12 anti-PL7 positive ASSD patients, the mean age at the first sign of clinical symptoms was 56.3 yrs, which was similar with our study, all presented with ILD, in which 9 were NSIP pattern, 2 were with OP pattern and 1 with obliterative bronchiolitis (BO) pattern(24). In another anti-PL7 positive ASSD cohort with 18 patients, all had myositis when first diagnosed, and 10 (55.6%) had ILD(25).

In an anti-PL12 positive ASSD cohort with 17 patients, the mean age when diagnosed was 60.3 yrs, all patients had ILD when diagnosed, 15 out of which were with NSIP pattern and 2 were with OP pattern, and 7 had mild myositis(26).

Another anti-PL12 positive ASSD cohort with 31 patients had a myositis prevalence of 52% (16/31) and ILD prevalence of 90% 28/31, 14 out of which were with a UIP pattern, 5 with NSIP pattern and 5 with OP pattern, confirmed histopathologically in 14 patients received surgical lung biopsy, or either evaluated by HRCT(27).

Studies with larger samples suggest different conclusions that ASSD with various ARS is relatively homogenous, however, the distribution and timing of myositis, ILD alone at onset, and rashes differ among patients. In a retrospective Japanese cohort of ASSD with 166 patients, the ILD alone at onset was 63% in OJ-positive group, 33% in PL12-positive group, 26% in EJ group, 14% in PL7 group, and 5% in JO1-positive group(11), and those with anti-Jo-1, anti-EJ, and anti-PL-7 developed myositis later if they had ILD alone at the time of disease onset. In the AENEAS cohort with 828 ASSD patients, characteristics of triad findings were similar and the onset mainly began with a single triad finding in all groups despite some differences in overall prevalence, and the PL7-positive group and EJ-positive group had a higher ILD prevalence compared with JO-positive group($P=0.001$, $P=0.005$, respectively), and EJ-positive group presented more with an acute onset (74%), which was defined as dyspnea progressing rapidly in 4 weeks from respiratory symptoms onset. Moreover, survival was not influenced by the distinct anti-ARS antibodies' positivity, suggesting that ASSD is a heterogeneous condition and antibody specificity only partially correlates with the clinical course(5).

However, the pulmonary function of ASSD-ILD responding to therapy, one of the disease behaviors, had never been studied before. The change of FVC, one of the most important factors of the ILD clinical course, had been used to classify ILD into reversible or progressive type in classification and clinical trials(28, 29). All patients had an improvement on FVC in our study after therapy, which means even without a presence of myositis, the positive ARS antibody is a treatable trait of steroids or immunosuppressants for ILD. The myositis prevalence showed no differences among the 5 groups, which made the FVC comparable between groups, for the respiratory muscle weakness has impact on the spirometry values, leading to a complicated interpretation(1). No standard treatment has been proposed for ASSD, however, prednisone should be the mainstay, with or without immunosuppressants (30), which was proved again by our study.

Anti-Ro52, a myositis associated antibody, the positive frequency of which was reported as 65% in an anti-Jo1 positive ASSD cohort(31). In our cohort the anti-Ro52 positive rate was 87.9% in Jo-1 group, and 91.3% in EJ group, respectively, which were significantly higher than the other 3 groups. The EJ group and the Jo1 group had the highest frequency of OP pattern, indicating the occurrence of OP might be correlated with the anti-Ro52 positivity.

Our study had some limitations. It was single center and retrospective, the sample was relatively small and the follow up time was not long enough. In another ASSD cohort the RP-ILD was statistically more prevalent in patients with positive anti-PL7 antibody than those without anti-PL7(3). The RP-ILD cases were not included in this study because the spirometry could not be performed when diagnosed due to the patients' weakness, and in our study the excluded 7 case of RP-ILD included 5 with EJ positive and 2 PL-7 positive. Shi's cohort, using a Solomon's criteria of ASSD, showed that a coincidence of anti-Ro52 antibody predicted RP-ILD(3). RP-ILD is more life threatening and needs more study in the future.

List Of Abbreviations

Anti-Synthetase Syndrome: ASSD

Aminoacyl tRNA synthetases: ARS

High Resolution Computer Tomography: HRCT

Forced vital capacity: FVC

Interstitial lung disease: ILD

Non-specific Interstitial Pneumonitis: NSIP

Organizing Pneumonia: OP

Usual Interstitial Pneumonia: UIP

Multidisciplinary discussion team: MDT

Polymyositis: PM

Dermatomyositis: DM

Declarations

Ethics approval and consent to participate:

Waived, because it was a retrospective analysis

Consent for publication:

Not applicable

Availability of data and materials:

Not applicable

Competing interests:

The authors declare that they have no competing interests

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Authors' contributions:

ZX designed the work, drafted the manuscript ; **YW** worked on data acquisition, **WY** worked on statistical analysis, **SX** worked in the MDT discussion as a rheumatologist, **LQ** interpreted the pathological findings in the MDT discussion, **GY** interpreted the pathological finding in the MDT, **YQ** revised the manuscript.

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Figures

Figure 1

The CT of a 50-year-old male ILD patient with anti-EJ-positive, showing ground glass opacity, and traction bronchiectasis.

Figure 2

Right lower lobe cryobiopsy of this 50-year-old patient showed chronic interstitial inflammation and granulation tissue formation in alveoli (hematoxylin-eosin staining, original magnification $\times 100$), in accordance with an organizing pneumonia (OP) pattern.

Figure 3

The CT of a 55-year-old male ILD patient with anti-PL7-positive, showing ground glass opacity, reticulation and traction bronchiectasis.

Figure 4

Right lower lobe cryobiopsy of this 55-year-old patient showed uniform chronic interstitial inflammation with lymphocyte infiltration and widened alveolar septum (hematoxylin-eosin staining, original magnification $\times 100$), in accordance with an nonspecific interstitial pneumonia (NSIP) pattern.