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# Clinical characteristics of patients with anti-aminoacyl-tRNA synthetase antibody positive idiopathic interstitial pneumonia

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## ARTICLE INFO

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## ABSTRACT

*Background:* Anti-aminoacyl-tRNA synthetase (ARS) antibodies have been detected in patients with polymyositis/dermatomyositis (PM/DM) and are especially correlated with interstitial lung disease (ILD). The aim of this study was to clarify the clinical features of patients with anti-ARS antibody positive idiopathic interstitial pneumonias (IIPs).

*Methods:* Patients were classified into three groups: 1) IIP with anti-ARS antibodies (ARS(+)IIP), 2) IIP without anti-ARS antibodies (ARS(−)IIP), and 3) PM/DM-associated ILD with anti-ARS antibodies (ARS(+)PM/DM-ILD). Clinical characteristics were compared retrospectively between the ARS(+)IIP group and the ARS(−)IIP group or ARS(+)PM/DM-ILD group.

*Results:* Eighteen ARS(+)IIP, 284 ARS(−)IIP, and 20 ARS(+)PM/DM-ILD patients were enrolled. The ARS(+)IIP group was significantly older and the male sex was predominant, had a lower prevalence of signs of connective tissue disease, differences in HRCT findings and patterns, and higher KL-6 levels compared to the ARS(+)PM/DM-ILD group. The findings in the bronchoalveolar lavage fluid (BALF) showing lymphocytosis and a lower CD4/CD8 ratio were similar between the two groups. However, the ARS(+)IIP group had significantly lower percentage of sputum, higher prevalence of mechanic's hand, higher KL-6 levels, lower percentage of vital capacity in the pulmonary function test, and lower CD4/CD8 ratio in BALF, compared to the ARS(−)IIP group.

*Conclusions:* The present study demonstrated that features of pulmonary involvement were similar to those in the ARS(+)PM/DM-ILD group; however, some differences including HRCT findings and higher KL-6 levels suggest that ARS(+)IIP has severe ILD compared with ARS(+)PM/DM-ILD. Further prospective studies with a larger number of patients will elucidate the exact role of anti-ARS antibodies in IIPs.

*Abbreviations:* ALD, aldolase; ARS, anti-aminoacyl-tRNA synthetase; ARS(−), anti-ARS antibody negative; ARS(+), anti-ARS antibody positive; ASS, anti-synthetase syndrome; BALF, bronchoalveolar lavage fluid; CADM, clinically amyopathic dermatomyositis; CK, creatine kinase; CT, computed tomography; CTD, connective tissue diseases; DAD, diffuse alveolar damage; HRCT, high-resolution computed tomography; IIP, idiopathic interstitial pneumonia; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; KL-6, Krebs von den Lungen 6; NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia; PM/DM, polymyositis/dermatomyositis; UIP, usual interstitial pneumonia; %VC, percentage of the vital capacity

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## 1. Introduction

Idiopathic interstitial pneumonias (IIPs) are diagnosed based on the involvement of the lung parenchyma with varying combinations of fibrosis and inflammation and exclusion of known causes of interstitial pneumonia, such as connective tissue diseases (CTD) [1,2]. Patients with IIP occasionally have clinical features that suggest an underlying autoimmune disease without meeting current criteria for the diagnosis of a particular CTD. This subset of interstitial lung diseases (ILD) has been classified into categories such as undifferentiated CTD-associated ILD [3], lung-dominant CTD [4], autoimmune-featured ILD [5], and interstitial pneumonia with autoimmune features (IPAF) [6].

Anti-aminoacyl-tRNA synthetase (ARS) antibodies that recognize cytoplasmic ARS are known as the most common myositis-specific antibodies detected in polymyositis/dermatomyositis (PM/DM). Eight anti-ARS antibodies have been identified thus far: anti-Jo-1, anti- PL-7, anti-PL-12, anti-EJ, anti-OJ, anti-KS, anti-Zo, and anti-Ha. PM/DM patients can be classified into subsets based on myositis-specific antibodies that are associated with clinically common features [7,8]. Patients with anti-ARS antibodies are associated with a unique subset of features characterized by inflammatory myopathy, arthritis, Raynaud's phenomenon, mechanic's hands, and ILD, called anti-synthetase syndrome (ASS) [9,10]. Although anti-ARS has been described mainly in PM/DM, detection of anti-ARS antibodies in rheumatoid arthritis or IIPs without myositis have also been reported [11–14]. Nevertheless, most studies on anti-ARS were performed in patients with PM/DM and the clinical characteristics of IIPs with anti-ARS antibodies are still unclear. The aim of this study was to clarify the clinical characteristics of patients with anti-ARS antibody positive IIPs by comparing those with IIPs without anti-ARS antibodies or PM/DM-ILD with anti-ARS antibodies.

## 2. Material and methods

### 2.1. Study population

Consecutive Japanese patients with IIP who visited the Department of Respiratory Medicine at Nagasaki University Hospital and the Hospital of the University of Occupational and Environmental Health and Japanese patients with PM/DM associated ILD (PM/DM-ILD) who visited the Department of Respiratory Medicine at Nagasaki University Hospital from 2008 to 2015, were retrospectively studied. The diagnosis of IIP was based on the clinical presentation during the first visit to our hospitals. IIP was defined as interstitial pneumonia of unknown cause where the patient did not fulfill classification criteria for any specific CTD or vasculitis. Lung diseases that were potentially caused by drug or occupational-environmental exposures were also excluded [1,2]. A clinical diagnosis of PM/DM was made according to Bohan and Peter's criteria [15,16]. A diagnosis of clinically amyopathic dermatomyositis (CADM) was made when a patient had typical skin manifestations such as Gottron's sign and a heliotrope rash without muscle symptoms and an elevation of serum myogenic enzymes during the observation period [17–19]. Patients were classified into three groups in this study. Patients with IIP were classified into the anti-ARS antibody positive (ARS(+)IIP) or negative (ARS(−)IIP) groups and anti-ARS antibody positive patients with PM/DM were defined as the ARS (+)PM/DM-ILD group. None of the patients with IIP with anti-ARS antibodies developed any additional finding of connective tissue disease during the observation period. Blood samples were collected from each patient during the primary visit and stored at −20 °C until use. For the anti-ARS antibody analysis, sera were analyzed by immunoprecipitation of $^{35}$S-methionine-labeled K562 cell extract; specificities of autoantibodies were determined by using specific reference sera [20].

All demographic and clinical information was obtained retrospectively from medical records at the time of the initial diagnosis. Acute exacerbation was defined as follows: 1) a previous or concurrent diagnosis of interstitial pneumonia, 2) acute worsening or development of dyspnea of typically < 1 month in duration, 3) computed tomography (CT) with new bilateral ground-glass opacity and/or consolidation superimposed on a background pattern, and 4) deterioration not fully explained by cardiac failure or fluid overload [21].

The study protocol was approved by the Human Ethics Review Committee at Nagasaki University School of Medicine and the Hospital of the University of Occupational and Environmental Health, Japan. A signed informed consent was obtained from all subjects in accordance with the Declaration of Helsinki and its subsequent modifications.

### 2.2. Evaluation of high-resolution computed tomography (HRCT) findings and patterns

Chest HRCT of all patients was retrospectively assessed by two pulmonologists (N.S. and H.I.). The pulmonologists recorded the following features seen on HRCT: the distribution and presence of reticulation, honeycombing, traction bronchiectasis, ground-glass attenuation, consolidation, thickening of bronchovascular bundles, small nodules, and pleural effusion. The HRCT patterns were classified according to the international classification of IIPs created by the American Thoracic Society/European Respiratory Society [2]. HRCT patterns included usual interstitial pneumonia (UIP), nonspecific interstitial pneumonia (NSIP), organizing pneumonia (OP), and diffuse alveolar damage (DAD). The classification of “others” was used when an HRCT finding did not meet the above patterns.

### 2.3. Statistical analysis

All values are expressed as medians (interquartile range) or the frequency (number). To clarify the characteristics of ARS(+)IIP group, differences between the ARS(+)IIP group and ARS(−)IIP group or ARS (+)PM/DM-ILD group were compared using the chi-squared test, Fisher's exact test, or the Steel test. Multiple pairwise group comparisons were performed to adjust the P value by using the Steel test or the Bonferroni correction for Fisher's exact test. In the Steel test, we set the ARS(+)IIP group as the investigated group and set the ARS(−)IIP and ARS(+)PM/DM-ILD groups as the control groups. Kaplan-Meier survival curves were constructed for the three group populations and comparisons were made using the log-rank test. A P value $< 0.05$ was regarded as statistically significant. All data were analyzed using JMP® Pro 11.2.0 (SAS Institute Inc., Cary, NC, USA).

## 3. Results

Three hundred and two consecutive Japanese patients with IIP who visited the Department of Respiratory Medicine at Nagasaki University Hospital or the Hospital of the University of Occupational and Environmental Health from 2008 to 2015 and 37 Japanese patients with PM/DM-ILD who visited the Department of Respiratory Medicine at Nagasaki University Hospital from 2008 to 2015, were enrolled.

### 3.1. Prevalence of anti-ARS antibodies

Anti-ARS antibodies were found in 18 (6.0%) of 302 patients with IIPs and in 20 (54.1%) of 37 patients with PM/DM-ILD. The specificities of the anti-ARS antibodies found in ARS(+)IIPs and ARS(+)PM/DM-ILD are shown in Table 1. Anti-Jo-1 was the most frequent antibody in both the ARS(+)IIP (N = 5, 27.8%) and ARS(+)PM/DM-ILD (N = 9, 45.0%) groups. Anti-KS was as common as the anti-Jo-1 antibody (N = 5, 27.8%) and anti-EJ antibody was detected in four patients (22.2%) in the ARS(+)IIP group. In the ARS(+)PM/DM-ILD group, anti-PL-7 antibody (N = 4, 20.0%) was the second most common antibody detected. The difference in the fine specificity of anti-ARS antibodies between these two groups was not significantly different (P = 0.581 by Fisher's exact test). Seven of 18 patients of ARS(+)IIP