Comparison of pulmonary involvement between patients expressing anti-PL-7 and anti-Jo-1 antibodies

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ABSTRACT

Anti-PL-7 is an anti-tRNA synthetase antibody (ARS) and interstitial lung disease (ILD) is the most frequent complication of anti-PL-7-associated antisynthetase syndrome (ASS). However, the features of ILD have not been fully elucidated. The present study retrospectively compares seven and 15 patients who were positive for anti-PL-7 and anti-Jo-1 antibodies, respectively. The features of ILD did not significantly differ between the two groups, but the ratio of lymphocytes in bronchoalveolar lavage fluid was higher in the Jo-1, than in the PL-7 group. High-resolution computed tomography revealed nonspecific interstitial pneumonia in all patients in the PL-7 group and organizing pneumonia in four of the 15 patients in the Jo-1 group. These findings suggest that pulmonary complications slightly differ between patients expressing anti-PL-7 and anti-Jo-1 antibodies. Further studies are required to clarify the features of ILD associated with PL-7.

Keywords: antisynthetase syndrome, interstitial lung disease, dermatomyositis, polymyositis

Introduction

Antisynthetase syndrome (ASS) is characterized as inflammatory myositis, fever, arthritis, Raynaud's phenomenon, mechanic's hands, and interstitial lung disease (ILD) associated with the expression of anti-tRNA synthetase antibodies (ARS) [1]. Anti-Jo-1 (anti-histidyl) antibody is the most common, but other anti-ARS including anti-PL-12, anti-PL-7, anti-OJ, and anti-EJ tRNA-synthetase antibodies are now routinely diagnosed in Europe using immunoblot assays [2]. Thus, the features of each ASS have become clearer [3, 4]. Interstitial lung disease associated with ARS is the most prevalent ASS manifestation and it is the main cause of morbidity and mortality in ASS [1, 3],[5]. Anti-PL-7 antibody is directed against threonyl-tRNA synthetase, and it accounts for 10% - 15% of all ARS cases [6]. Interstitial lung disease is the most frequent complication of anti-PL-7-related ASS, occurring in 80% of patients [6], but the features have not been fully elucidated. On the other hand, ILD in patients with anti-Jo-1 antibody has been described in detail [7-9]. Here, we aimed to clarify the features of ILD by comparing patients expressing anti-PL-7 and anti-Jo-1 antibodies.

Materials and methods

Study population

The medical records of seven consecutive patients expressing anti-PL-7 and 14 expressing anti-Jo-1 who were admitted to Nagasaki University Hospital between November 2001 and March 2013 were retrospectively analyzed. Polymyositis and dermatomyositis (PM/DM) were diagnosed based on the Bohan and Peter criteria [10], and DM was distinguished from PM by the presence of a heliotrope rash or Gottron’s lesions. The diagnosis of CADM was based on the criteria proposed by Sontheimer [11], namely clinical skin manifestations typical of DM but minimal or absent clinical features of myositis for >2 years after the onset of skin manifestations. Serum anti-PL-7 antibody was measured using RNA immunoprecipitation

assays [3] (n = 6) or a Myositis Profile 3 EuroLine immunoblot assay (Euroimmun, Lübeck, Germany) (n = 1). Serum anti-Jo-1 antibody was determined using an enzyme-linked immunosorbent assay (SRL Inc., Tokyo, Japan).

Evaluation of ILD

All patients were assessed by chest radiography and high-resolution computed tomography (HRCT). Two independent observers who were unaware of the patients' profiles categorized the HRCT findings as organizing pneumonia (OP) with peribronchial or subpleural consolidation or ground-glass opacities without fibrosis, or as nonspecific interstitial pneumonia (NSIP) characterized by patchy or diffuse ground-glass opacities with associated reticular opacities, traction bronchiectasis, and bronchiolectasis. Divergent conclusions were resolved by consensus between the two observers. Pulmonary function results were considered abnormal when the ratio (%) of vital capacity (%VC) and the ratio (%) of diffusing capacity for carbon monoxide (%DLCO) were < 80%. Bronchoalveolar lavage (BAL) fluid was collected with three instillations of sterile physiological saline (50 mL) through a flexible bronchoscope as described [12]. Differential cell counts in BAL were evaluated according to the American Thoracic Society Guidelines; lymphocytes > 15%, neutrophils > 3%, and eosinophils > 1% were considered excessive [13]. Responses to ILD therapy were evaluated according to the criteria for idiopathic pulmonary fibrosis [14]. The Human Ethics Review Committee of Nagasaki University School of Medicine approved the study protocol.

Statistical analysis

All values are expressed as means ± SD unless otherwise stated. Differences between groups were compared using an unpaired t-test for means and Fisher's exact test for counts. Values

with $P < 0.05$ were regarded as significantly different.

Results

Clinical features of patients with anti-PL-7 antibody

Table 1 shows the clinical features at the time of the first presentation determined from the seven female patients (age, 47 ± 14 years) expressing anti-PL-7 antibody. All clinical data including CT findings were obtained before treatment with prednisolone and immunosuppressants. Muscle involvement, Raynaud's phenomenon, and mechanic's hand were evident in 3, 3 and 2 of them, respectively. Laboratory findings showed elevated levels of creatine kinase (CK) and of Krebs von den Lungen (KL-6) protein in four and in all seven patients, respectively. Chest HRCT revealed NSIP in all patients. A surgical lung biopsy from one patient confirmed NSIP. Pulmonary function tests showed restrictive (5/7 patients) and diffusive (5/6 patients) types, but not obstructive impairment (data not shown). Ratios of lymphocytes, neutrophils, and eosinophils were elevated in BAL fluid from 5, 6 and 7 patients, respectively, and CD4/CD8 ratios were lower in five of the seven patients. Five patients were treated with prednisolone and an immunosuppressant, one received prednisolone alone, and one was not treated. The clinical course of ILD improved, stabilized, and deteriorated in 2, 2 and 3 patients, respectively.

Comparison of features between patients expressing anti-Jo-1 and anti-PL-7 antibodies

We compared the characteristics including pulmonary involvement between patients expressing anti-Jo-1 and anti-PL-7 antibodies. Table 2 shows the clinical characteristics at initial presentation. Sex, age, and smoking history, as well as pulmonary, muscle and skin findings did not significantly differ between the two groups. Raynaud's phenomenon was statistically more prevalent in the PL-7 group, whereas other symptoms including dyspnea,

cough and fever were not. The frequency of clinical diagnoses including DM, PM, CADM, and ILD without skin and muscle symptoms did not differ. One and two patients in the PL-7 Jo-1 groups, respectively, also had Sjögren's syndrome. Preceding pulmonary or skin/muscle symptoms also did not differ. Table 3 shows the clinical parameters at initial presentation. Markers of ILD including serum KL-6, surfactant protein (SP)-D, SP-A, and LDH, as well as levels of the muscle enzymes CK and aldolase did not differ between the groups. Arterial blood gas analysis in room air revealed significant decreased levels of PaO_2 in the Jo-1, compared with the PL-7 group. The results of pulmonary function tests (%VC, FEV1/FVC%, and %DLCO) did not differ between the groups. The ratio of lymphocytes was significantly elevated in BAL fluid from the Jo-1 group. The proportions of patients with > 15% lymphocytes, > 5% neutrophils and > 1% eosinophils in BAL fluid did not differ between the groups. The HRCT findings such as ground grass opacity and reticular shadows were common to both groups at a lower and peripheral predominance. All patients in the PL-7 group had signs of NSIP, whereas four patients in the Jo-1 group had signs of OP. Traction bronchiectasis was more prevalent in the PL-7, than in the Jo-1 group (100% vs. 64.3%), but the difference did not reach significance. Other findings were essentially the same between the two groups. The only clinical parameter that differed between the NSIP and OP findings in the Jo-1 group was a lower PaO_2 in OP (data not shown). The clinical course of pulmonary involvement was also evaluated. The median follow-up was longer for patients with PL-7 than with Jo-1 (68 vs. 30 months), but the difference did not reach significance. Most patients in both groups were treated with prednisolone and immunosuppressants. One patient in the PL-7 group received only long-term oxygen therapy. None of the patients died during the follow-up period. The clinical course of pulmonary involvement, as well as %VC and %DLCO did not differ between the groups, although only half of the Jo-1 group could be evaluated (data not shown).

Discussion

We compared patients expressing anti-PL-7 and anti-Jo-1 antibodies to elucidate the features of ILD in patients expressing anti-PL-7 antibody, which was associated with several features of ILD.

Chest CT findings of all patients expressing anti-PL-7 showed signs of NSIP. Previous studies of ILD associated with anti-PL-7-related ASS have described pulmonary HRCT findings as NSIP, OP and usual interstitial pneumonia (UIP), with the most prevalent findings being NSIP [4]. Pulmonary HRCT findings of patients with anti-PL-7 predominantly showed NSIP (43-75%) [6],[15]. The finding of UIP in pulmonary HRCT of patients expressing anti-Jo-1 is reportedly associated with ILD deterioration, whereas the OP finding in such patients is not [9]. Further studies are needed to determine whether or not chest CT findings can predict the prognosis of patients expressing anti-PL-7.

The differential cell findings in BAL fluid revealed a higher proportion of lymphocytes in the Jo-1 group. A study of 12 patients expressing anti-PL-7 found increased numbers of neutrophils (n = 5) or lymphocytes (n = 3) in BAL fluid from eight patients, indicating alveolitis [15]. One study found an elevated ratio of neutrophils in BAL fluid from a group of patients with progressive PM/DM, while that of lymphocytes remained normal [16].

A previous study found a poorer outcome of ILD for patients expressing anti-PL-7 and PL-12 compared with anti-Jo-1 [17]. Furthermore, five-year survival rates were lower for those expressing anti-PL-7 than anti Jo-1 (67% vs. 90%) and pulmonary causes of death (pulmonary fibrosis and pulmonary hypertension) were common in patients expressing anti-Jo-1 (19/36; 53%) and anti-PL-7 (11/14; 79%) [18]. The HRCT findings of NSIP and neutrophilic inflammation in the lungs might be related to poorer survival for patients expressing anti-PL-7 compared with anti-Jo-1.

The present study is limited by the small patient cohort and by potential selection bias

resulting from measuring anti-Jo-1 Ab and anti-PL-7 Ab. Anti-Jo-1 Ab is routinely and measured commercially when CVD-IP is suspected in the Japanese clinical setting. Thus, anti-Jo-1 Ab our institution is routinely measured in patients who present at our institution with interstitial pneumonias that mimic interstitial lung disease associated with antisynthetase syndrome. On the other hand, anti-PL-7 Ab is measured in university, not commercial laboratories, when antisynthetase syndrome and anti-Jo-1 Ab negative status is suspected.

The present study found a slight difference in pulmonary complications between patients expressing anti-PL-7 and anti-Jo-1 antibodies. Further studies are required to define the features of pulmonary complications in patients expressing anti-PL-7 antibodies.

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Conflict Interest: None

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Table 1. Characteristics of patients with anti-PL-7 antibody.

	1	2	3	4	5	6	7
Sex (F/M)	F	F	F	F	F	F	F
Age (y)	55	51	28	62	54	25	53
Muscle involvement	+	+	-	-	-	+	-
Raynaud's phenomenon	-	-	+	+	+	-	-
Mechanic's hand	-	+	-	-	+	-	-
CK (IU/L)	1632	1409	154	1988	68	1025	77
KL-6 (U/mL)	1000	833	2155	1770	1460	1010	538
HRCT pattern	NSIP	NSIP	NSIP	NSIP	NSIP	NSIP	NSIP
%VC	54.8	58.3	67.9	56.6	108.4	62.2	90.2
%DLCO	42.1	33.8	47.7	49.5	81.1	ND	71.6
BALF findings							
Lymphocytes (%)	21.1	40.7	20.8	55.1	33.0	12.1	14.6
Neutrophils (%)	34.3	37.4	7.7	1.4	3.9	5.7	7.8
Eosinophils (%)	9.0	11.8	7.1	1.9	1.4	3.8	8.9
CD4/CD8	0.3	0.5	0.2	7.7	2.3	0.03	0.8
Therapy	P, IM	P, IM	P, IM	P, IM	-	P	P,IM
Clinical course (I/S/D)	S	I	D	I	D	D	S

I, improvement; D, deterioration; IM, immunosuppressant; ND, no data.
P, prednisolone; S, stable.

Table 2. Comparison of clinical characteristics of patients with anti-PL-7 and anti-Jo-antibodies.

	PL-7 (N = 7)	Jo-1 (N = 14)	p
Sex (M:F)	0:7	3:11	0.27
Age	47 ± 14	55 ± 12	0.23
Smoking history	0 (0%)	5 (35.7%)	0.10
Symptoms			
Dyspnea	4 (57.1%)	2 (16.7%)	0.64
Cough	4 (57.1%)	13 (92.9%)	0.09
Fever	3 (42.9%)	2 (14.3%)	0.18
Raynaud's phenomenon	3 (42.9%)	0 (0%)	0.03
Physical findings			
Fine crackle	6 (85.7%)	11 (78.6%)	0.59
Muscle weakness	2 (28.6%)	6 (42.9%)	0.44
Polyarthritis	2 (28.6%)	3 (21.4%)	0.56
Heliotrope	2 (28.6%)	1 (7.1%)	0.25
Gottron's papules	3 (42.9%)	3 (21.4%)	0.30
Mechanic’s hand	2 (28.6%)	3 (21.4%)	0.56
Clinical diagnosis (DM/PM/CADM/IP)	5/0/2/0	5/2/5/2	0.35
Other CTD	SjS 2	SjS 1	
Preceding symptoms (Lung/skin・muscle/simultaneous)	3/2/2	7/6/1	0.41

CADM, clinically amyopathic dermatomyositis; CTD, connective tissue disease.
DM, dermatomyositis; I, immunosuppressant; PM, polymyositis; PSL, prednisolone

Table 3. Comparison of clinical parameters between patients with anti-PL-7 and anti-Jo-1 antibodies.

	PL-7	Jo-1	p
Laboratory findings	N = 7	N = 14	
KL-6 (U/mL)	1351 ± 664	675 ± 502	0.30
SP-D (ng/mL)	238 ± 161	171 ± 27	0.99
SP-A (ng/mL)	86.6 ± 37.2	56.7 ± 0.4	0.59
LDH (IU/L)	286 ± 129	372 ± 97.6	0.82
CK (IU/L)	739 ± 900	1082 ± 974	0.77
Aldolase (IU)	16.4 ± 14.6	37.5 ± 13.4	0.66
PaO_2 (Torr)	87.7 ± 7.6	82.2 ± 10.6	0.02
Pulmonary function tests	N=7	N=10	
%VC	76.3 ± 22.4	69.0 ± 24.4	0.27
FEV1/FEV% (%)	86.1 ± 4.8	84.9 ± 5.5	0.19
%DLCO	56.7 ± 19.2	45.1 ± 11.9	0.69
BALF cell findings	N = 7	N = 13	
Total cells (x 10^5/mL)	2.6 ± 2.0	9.7 ± 0.8	0.18
Macrophages (%)	49.1 ± 24.8	15.4 ± 13.6	0.18
Lymphocytes (%)	32.8 ± 16.1	71.7 ± 4.7	0.04
Neutrophils (%)	11.6 ± 14.7	6.6 ± 7.8	0.73
Eosinophils (%)	6.2 ± 4.5	6.0 ± 0.7	0.66
CD4/CD8	2.3 ± 3.1	0.2 ± 0.3	0.32
CT findings	N = 7	N = 14	
Ground glass opacity	6 (85.7%)	14 (100%)	0.33
Reticular shadow	7 (100%)	12 (85.7 %)	0.43
Consolidation	2 (28.6%)	8 (57.1 %)	0.22
Peribronchovascular thickening	0 (0%)	0 (0%)	1.00
Traction bronchiectasis	7 (100%)	9 (64.3%)	0.10
Honeycombing	0 (0%)	0 (0%)	1.00
Predominance (upper/lower)	0/7	2/12	0.43
Predominance (peripheral/central)	7/0	13/1	0.67
NSIP/OP	7/0	10/4	0.17

NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia.