

High Prevalence of Acute Exacerbation of Interstitial Lung Disease in Japanese Patients with Systemic Sclerosis

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Systemic sclerosis (SSc) is a systemic autoimmune disease characterized by extensive fibrosis and autoantibodies. Its clinical manifestations are diverse and include Raynaud's phenomenon, gastrointestinal dysmotility, interstitial lung disease (ILD), pulmonary hypertension, and renal crisis. Among these, ILD is the primary cause of SSc-related death. It has been considered that acute exacerbation of ILD (AE-ILD) is not common in patients with SSc; however, little is known about the prevalence of AE-ILD in Japanese patients with SSc. In this study, we aimed to clarify the prevalence, clinical characteristics, and prognosis of patients with SSc who developed AE-ILD and to identify predictive factors for AE-ILD in our Japanese cohorts. Clinical data of patients who visited our department from 1990 to 2014 and fulfilled the 2013 classification criteria for SSc were retrospectively reviewed. A total of 139 patients were enrolled. The mean age of onset was 49.1 years, and 113 (81.3%) patients were female; 116 (83.5%) had limited cutaneous involvement, and the overall 10-year survival rate was 92.0%. Among 66 (47.5%) patients with ILD, 13 (9.4%) developed AE-ILD. Patients with AE-ILD had a significantly higher incidence of overlap with polymyositis (PM) or dermatomyositis (DM) and lower prevalence of anticentromere antibodies with higher mortality rate compared with those without AE-ILD. Multivariate Cox regression analysis identified that an overlap with PM or DM was the most significant predictive factor for AE-ILD. Our study results suggest that Japanese patients with SSc, particularly patients overlapped with PM or DM, have a high risk of AE-ILD.

Keywords: acute exacerbation; interstitial lung disease; overlap; polymyositis/dermatomyositis; systemic sclerosis
Tohoku J. Exp. Med., 2016 August, 239 (4), 297-305. © 2016 Tohoku University Medical Press

Introduction

Systemic sclerosis (SSc) is a complex autoimmune disorder characterized by extensive fibrosis, vascular alterations, and autoantibodies (Gabielli et al. 2009; Broen et al. 2014). SSc can affect almost any internal organ, and its clinical manifestations include Raynaud's phenomenon, gastrointestinal dysmotility, interstitial lung disease (ILD), pulmonary hypertension, and renal crisis. SSc is generally divided into two disease subsets based on the extent of skin sclerosis (LeRoy et al. 1988). One is limited type, in which skin thickening is limited to the areas distal to the elbows. The other is diffuse type, in which skin sclerosis extends proximal to the elbows (LeRoy et al. 1988). Patients with diffuse type have a high incidence of ILD, renal crisis, and gastrointestinal involvement; in contrast, patients with limited type frequently develop pulmonary hypertension (Gabielli et al. 2009; Broen et al. 2014).

A variety of autoantibodies have been identified in patients with SSc (Nihtyanova and Denton 2010). Anti-topoisomerase I antibody is associated with diffuse type and ILD, whereas anticentromere antibody is frequently detected in patients with limited type and pulmonary hypertension. Patients with positive anti-RNA polymerase III antibody have an increased risk of renal crisis and malignancies (Joseph et al. 2014; Moinzadeh et al. 2014). In addition to these antibodies, the anti-U1 ribonucleoprotein (RNP) antibody is occasionally found in patients who have features of other connective tissue disease named overlap syndrome (Kaji et al. 2014; Moinzadeh et al. 2015).

The causes of death in patients with SSc have dramatically changed over the past 30 years (Ioannidis et al. 2005; Steen and Medsger 2007). ILD, which occurs at a frequency of 34%-60% in patients with SSc (Meyer et al. 2007; Hunzelmann et al. 2008; Hashimoto et al. 2012), is currently the primary cause of SSc-related death (Ioannidis

Received April 9, 2016; revised and accepted July 15, 2016. Published online August 3, 2016; doi: 10.1620/tjem.239.297.

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et al. 2005; Steen and Medsger 2007). However, no agents have been proven to effectively control ILD (Wells and Denton 2014). Cyclophosphamide was demonstrated to stabilize lung function in a randomized controlled trial, but its beneficial effect disappeared at 24 months (Tashkin et al. 2006; Tashkin et al. 2007). Moreover, acute exacerbation of ILD (AE-ILD) occurs at a 1-year frequency of 1.25%–3.3% and at a lifetime incidence of 7.2%, with a high mortality rate in patients with connective tissue disease (Park et al. 2007; Suda et al. 2009). Given the chronic nature of the disease, it has been considered that AE-ILD is not common in patients with SSc (Fan et al. 2014; Cappelli et al. 2015), but recent papers suggest that AE-ILD may occur even in patients with SSc (Park et al. 2007; Bussone and Mouthon 2011; Tachikawa et al. 2012; Ando et al. 2013; Yasuoka 2016). However, little data are available regarding the prevalence of AE-ILD in Japanese patients with SSc.

Therefore, the aims of this study were to clarify the prevalence, clinical characteristics, treatment, and prognosis of Japanese patients with SSc who developed AE-ILD and to identify predictive factors for AE-ILD.

Materials and Methods

Study design

In this study, we enrolled 139 Japanese patients with SSc who visited our department from April 1990 to June 2014. All patients fulfilled the 2013 classification criteria (van den Hoogen et al. 2013). The follow-up period was defined as the time from the initial manifestation of SSc-related symptoms to either the date of death or the latest visit to our hospital. All patients were followed up until January 2015. The study protocol was approved by the ethics committees of Tohoku University Graduate School of Medicine and performed in accordance with the Declaration of Helsinki.

Clinical data

We retrospectively reviewed medical records and obtained data regarding the age of onset, gender, autoantibodies, physical findings, organ involvement, overlap of other connective tissue disease, history of malignancies, medications, and prognosis. The maximum values of Krebs von den Lungen-6 (KL-6) during the follow-up were also obtained. Limited or diffuse type was defined by the area of skin sclerosis, as previously described (LeRoy et al. 1988).

Autoantibodies

Anti-topoisomerase I antibody, anticentromere antibody, and anti-U1-RNP antibody were examined in all patients. Anti-RNA polymerase III antibody was tested only when patients had negative results for those autoantibodies.

Evaluation of ILD

The presence and progression of ILD were evaluated by radiologists using high-resolution computed tomography (HRCT). Follow-up CT scans were performed when patients experienced a worsening of respiratory symptoms or the serum KL-6 levels increased. We divided progression of ILD into three categories; no progression, slow progression, and acute exacerbation. The definition of acute exacerbation or AE-ILD included a prior diagnosis of ILD, worsening of dyspnea within 1 month, new ground-glass opacities on

HRCT, hypoxemia, and the exclusion of other causes for the worsening symptoms (Collard et al. 2007). If repeated CT scan showed progression without fulfilling the definition of AE-ILD, we defined it as slow progression.

Other organ involvement

With regard to reflux esophagitis, we included patients who received proton pump inhibitors for treating symptoms related to gastrointestinal dysmotility. Pulmonary hypertension was defined as a mean pulmonary artery pressure of ≥ 25 mmHg, which was confirmed by right-heart catheterization. Scleroderma renal crisis was diagnosed with renal biopsy (Nihtyanova et al. 2014).

Diagnosis of other connective tissue disease

The diagnoses of rheumatoid arthritis and Sjögren's syndrome were based on the 2010 criteria (Aletaha et al. 2010) and the 1999 Japanese Ministry of Health and Welfare's diagnostic criteria (Fujibayashi et al. 2004), respectively. The criteria of Bohan and Peter (Bohan and Peter 1975) were used to diagnose polymyositis (PM) and dermatomyositis (DM). With regard to the diagnosis of PM and DM, we included definite diagnosis alone.

Treatment of ILD

If patients with SSc had progressive ILD, we initially administered a moderate dose (up to 0.6 mg/kg/day) of oral prednisolone (PSL). When the progression of ILD was evident despite the administration of oral PSL, we intensified immunosuppressive therapy, including high-dose (up to 1 mg/kg/day) oral PSL, methylprednisolone pulse therapy, intravenous cyclophosphamide (IVCY), calcineurin inhibitor (CI), and rituximab sometimes in combination.

Statistical analysis

Statistical analysis was performed using Graph Pad Prism 5 (San Diego, CA, USA) and EZR software (Kanda 2013), as previously described (Ishizuka et al. 2016; Yoshida et al. 2016). The Fisher's exact test was used for binary data, and the Mann-Whitney *U*-test was used for continuous data. Using the Kaplan-Meier method, the survival curves were drawn for a maximum of 10 years for each patient, and the log-rank test was used to compare the survival rates between patient groups. Stratified Cox regression analysis with a forward stepwise variable selection method was used to analyze any predictive factors. Variables with *p* values less than 1.0 in a univariate analysis were applied to the multivariate analysis. *P* values less than 0.05 were considered to be statistically significant.

Results

Demographic and baseline characteristics of patients with SSc

A total of 139 patients were enrolled. Baseline characteristics of the patients are shown in Table 1. The mean age of onset was 49.1 ± 15.1 years, and 81.3% of those patients were female. Anticentromere antibody was the most commonly identified autoantibody. Most of the patients (86.3%) experienced Raynaud's phenomenon, whereas ILD was observed in 66 patients (47.5%).

Table 1. Baseline characteristics of enrolled patients with systemic sclerosis.

Variables	All patients n = 139	Limited type n = 116	Diffuse type n = 23	P value	
Age of onset, year (Mean \pm SD)	49.1 \pm 15.1	50.6 \pm 13.9	41.1 \pm 18.1	0.027	
Female	113 (81.3)	97 (83.6)	16 (69.6)	0.14	
Autoantibodies	Anti-topoisomerase I	37 (26.6)	27 (23.3)	10 (43.5)	0.068
	Anticentromere	63 (45.3)	59 (50.9)	4 (17.4)	0.0051
	Anti-U1-RNP	23 (16.8)	16 (13.8)	7 (30.4)	0.065
Organ involvements	Raynaud's phenomenon	120 (86.3)	101 (87.1)	19 (82.6)	0.52
	Digital ulcer	34 (24.5)	22 (20.8)	12 (52.2)	0.0036
	Nail fold bleeding	57 (41.0)	45 (38.8)	12 (52.2)	0.25
	Reflux esophagitis	68 (48.9)	54 (44.6)	18 (78.3)	0.0061
	Interstitial lung disease	66 (47.5)	48 (41.4)	18 (78.3)	0.0013
	Pulmonary hypertension	9 (6.5)	7 (6.0)	2 (8.7)	0.64
Scleroderma renal crisis	5 (3.6)	3 (2.8)	2 (8.7)	0.19	
Malignancy	21 (15.1)	18 (15.5)	3 (13.0)	1.0	

n, (%). P values were determined by comparison between limited and diffuse type.

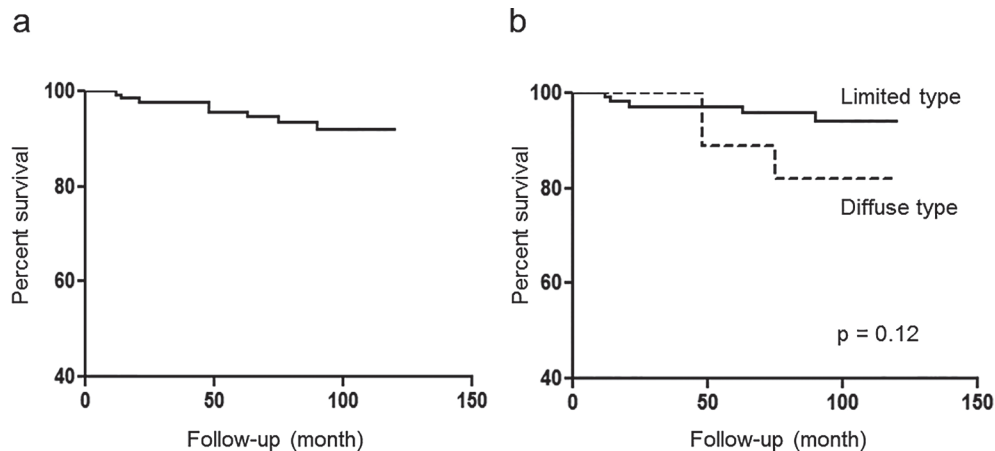


Fig. 1. Survival curve of patients with systemic sclerosis (SSc).

(a) Overall survival curve of 139 patients with SSc. (b) Survival curves of patients with limited (n = 116) and diffuse (n = 23) type.

Comparison of clinical characteristics between patients with limited and diffuse type

Of the 139 patients, 116 (83.5%) were diagnosed with limited type. When we compared the clinical features between the two groups, patients with limited type had a significantly higher age of onset, a higher rate of anticentromere antibody, and a lower incidence of digital ulcers, reflux esophagitis, and ILD (Table 1).

Overlap of other connective tissue disease

A total of 28 (20%) patients had an overlap with Sjögren's syndrome, 15 (10%) with rheumatoid arthritis, and 8 (5.8%) with PM or DM (hereafter we refer to as PM/DM). There were no significant differences in the prevalence of these coexisting diseases between patients with limited and diffuse type.

Survival rates

The overall survival rates for 139 patients were 99.2%, 95.7%, and 92.0% at 1, 5, and 10 years, respectively (Fig. 1a). The survival rate in patients with diffuse type tended to be lower than that in patients with limited type ($p = 0.12$, Fig. 1b).

Radiological patterns of ILD

Although CT scans were not available for two patients, the most common radiological finding of ILD was non-specific interstitial pneumonia, followed by usual interstitial pneumonia and organizing pneumonia (Fig. 2a).

Clinical characteristics of patients who developed ILD

Next, we compared clinical characteristics between patients with or without ILD (Table 2). Patients with ILD had a significantly higher KL-6 values and higher rates of anti-topoisomerase I antibody and renal crisis. The survival

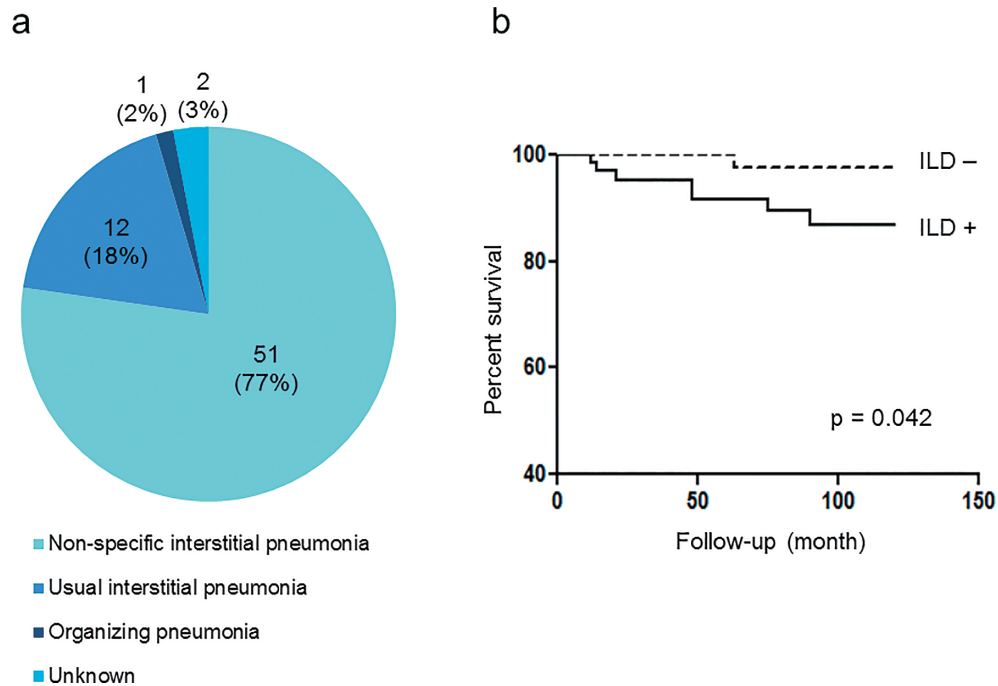


Fig. 2. Radiological findings of interstitial lung disease (ILD) and survival curves of patients with or without ILD. (a) Radiological patterns of ILD observed in 66 patients. (b) Survival curves of patients with (n = 66) or without ILD (n = 73).

Table 2. Comparison between patients with or without interstitial lung disease (ILD).

Variables	ILD + n = 66	ILD - n = 73	P value
Age of onset, year (Mean \pm SD)	49.2 \pm 14.8	48.9 \pm 15.3	0.94
Female	51 (82.3)	62 (84.9)	0.82
Limited type	48 (72.7)	68 (93.2)	0.0013
KL-6 (U/mL) (Median, range)	1,342 (201 - 7,974)	267 (100 - 1,260)	< 0.0001
Autoantibodies			
Anti-topoisomerase I	30 (45.5)	7 (9.6)	< 0.0001
Anticentromere	10 (15.2)	53 (72.6)	< 0.0001
Anti-U1-RNP	11 (16.7)	12 (16.4)	1.0
Organ involvements			
Raynaud's phenomenon	55 (83.3)	65 (89.0)	0.46
Digital ulcer	20 (30.3)	14 (19.2)	0.17
Nail fold bleeding	25 (44.6)	32 (43.8)	1.0
Reflux esophagitis	34 (51.5)	34 (46.6)	0.61
Pulmonary hypertension	6 (9.1)	3 (4.1)	0.31
Scleroderma renal crisis	5 (7.6)	0 (0.0)	0.022
Malignancy	13 (19.7)	8 (11.0)	0.16

n, (%).

rate in patients with ILD was significantly lower than that in patients without ILD (Fig. 2b).

Progression of ILD

Among the 66 patients who developed ILD, 55 patients (83%) underwent repeated CT scans. Of these patients, 22 patients showed no progression after a mean duration of 55 months (Fig. 3a). However, 33 patients demonstrated radiological progression of ILD after an aver-

age duration of 23 months. Among them, 13 patients fulfilled the definition of AE-ILD. Thus, the prevalence of AE-ILD was 9.4% (13/139).

Clinical characteristics of patients who developed AE-ILD

Then, we compared clinical features between patients with AE-ILD and those without AE-ILD (Table 3). The patients with AE-ILD had significantly higher values of KL-6, a lower rate of anticentromere antibody, and greater

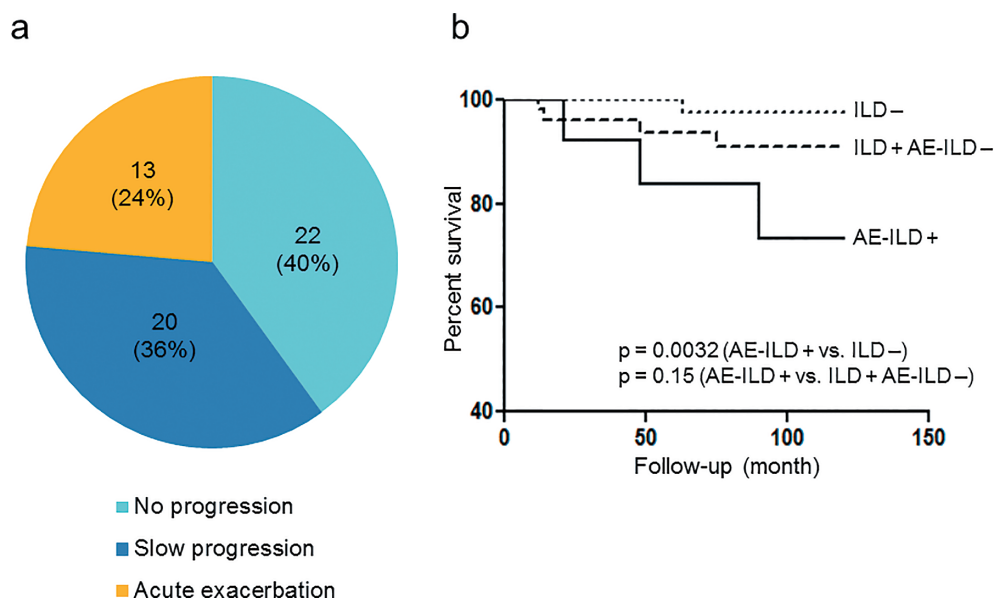


Fig. 3. Frequency of progression of interstitial lung disease (ILD) and comparison of survival rates between the groups sorted by ILD and acute exacerbation.

(a) Frequency of ILD progression among 55 patients who underwent repeated CT scans. The data from 11 out of 66 patients with ILD were not available. (b) Survival curves of patients who experienced acute exacerbation of ILD (AE-ILD+, $n = 13$), patients who had non- or slowly-progressive ILD (ILD+ AE-ILD-, $n = 53$), and patients who did not develop ILD (ILD-, $n = 73$).

Table 3. Comparison between patients with or without acute exacerbation of interstitial lung disease.

Variables	Acute exacerbation + $n = 13$	Acute exacerbation - $n = 126$	P value
Age of onset, year (Mean \pm SD)	49.3 \pm 12.7	49.0 \pm 15.3	0.87
Female	10 (76.9)	103 (81.7)	0.71
Limited type	9 (69.2)	107 (84.9)	0.23
KL-6 (U/mL) (Median, range)	2,313 (870 - 5,784)	403 (100 - 7,974)	< 0.0001
Autoantibodies			
Anti-topoisomerase I	4 (30.8)	33 (26.2)	0.75
Anticentromere	2 (15.4)	61 (48.4)	0.037
Anti-U1-RNP	3 (23.1)	20 (15.9)	0.45
Organ involvements			
Raynaud's phenomenon	11 (84.6)	109 (86.5)	0.69
Digital ulcer	3 (23.1)	31 (24.6)	1.0
Nail fold bleeding	6 (46.2)	51 (40.5)	0.77
Reflux esophagitis	5 (38.5)	63 (50.0)	0.56
Pulmonary hypertension	2 (15.4)	7 (5.6)	0.20
Scleroderma renal crisis	0 (0.0)	5 (4.1)	1.0
Overlap			
Polymyositis/dermatomyositis	3 (23.1)	5 (4.0)	0.028
Malignancy	1 (7.7)	20 (15.9)	0.69

n, (%).

incidence of overlap with PM/DM than the patients without AE-ILD. There was no significant difference in the prevalence of overlap with Sjögren's syndrome and rheumatoid arthritis between the two groups. Fig. 3b showed the survival curves of three groups: patients without ILD, patients with AE-ILD, and patients without AE-ILD. The survival rate of patients with AE-ILD was significantly lower than that of patients without ILD ($p = 0.0032$). A decreased

trend was observed in patients with AE-ILD, compared to those without AE-ILD ($p = 0.15$).

Treatment of ILD

Among the 66 patients with ILD, 49 (74%) patients received immunosuppressive therapy (Fig. 4a). Of these, 20 patients received oral PSL alone, whereas the rest of the patients received other immunosuppressive agents. When

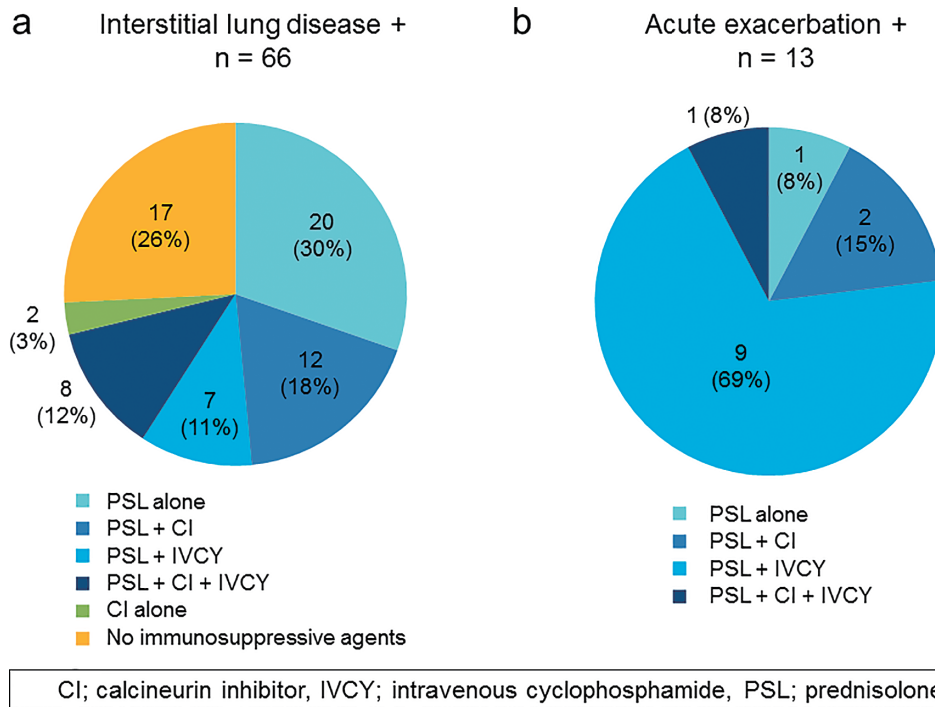


Fig. 4. Treatment of patients with interstitial lung disease (ILD). (a) Overall treatment of patients with ILD (n = 66). (b) Treatment for patients who developed acute exacerbation of ILD (n = 13). CI, calcineurin inhibitor; IVCY, intravenous cyclophosphamide; PSL, prednisolone.

Table 4. Multivariate Cox regression analysis for acute exacerbation of interstitial lung disease.

Variables	Adverse factor	Univariate		Multivariate	
		HR (95% CI)	P value	HR (95% CI)	P value
Age of onset	+1	10.24 (0.982 - 1.068)	0.27		
Gender	male	1.559 (0.4284 - 5.676)	0.50		
Limited / diffuse type	diffuse type	2.005 (0.6126 - 6.559)	0.25		
Anti-topoisomerase I	positive	1.124 (0.345 - 3.662)	0.85		
Anticentromere	positive	0.2721 (0.06011 - 1.231)	0.09	0.3065 (0.0673 - 1.396)	0.13
Anti-U1-RNP	positive	1.339 (0.3639 - 4.927)	0.66		
Raynaud's phenomenon	positive	0.8641 (0.191 - 3.908)	0.85		
Reflux esophagitis	positive	0.6955 (0.232 - 2.085)	0.52		
Digital ulcer	positive	0.9305 (0.2558 - 3.384)	0.91		
Pulmonary hypertension	positive	2.122 (0.4672 - 9.638)	0.33		
Malignancy	positive	0.386 (0.05012 - 2.973)	0.36		
Overlap with Sjögren's syndrome	positive	1.534 (0.4704 - 5.001)	0.48		
Overlap with rheumatoid arthritis	positive	1.152 (0.254 - 5.222)	0.85		
Overlap with polymyositis/dermatomyositis	positive	8.084 (2.107 - 31.01)	0.0023	6.973 (1.8050 - 26.930)	0.0049

CI, confidence interval; HR, hazard ratio.

limited to the patients who developed AE-ILD (Fig. 4b), most of the patients received combination therapy. However, 6 out of 13 patients (46%) died during follow-up.

Multivariate analysis of predictive factors for AE-ILD

We performed multivariate Cox regression analysis to clarify the predictive factors for AE-ILD (Table 4). The age of onset, gender, disease subsets, autoantibodies, organ involvement, malignancies, and overlap with connective tissue disease were employed in this analysis. Univariate analysis suggested that anticentromere antibody and the overlap with PM/DM were significant variables; however, multivariate analysis showed that the most important predictive factor was the overlap with PM/DM ($p = 0.0049$).

Discussion

In this study, we retrospectively analyzed the clinical characteristics of 139 Japanese SSc patients and demonstrated that the prevalence of AE-ILD was 9.4% and that coexisting PM/DM was the most significant predictive factor. To our knowledge, this is the first study that showed the prevalence, clinical characteristics, outcome, and predictive factor of AE-ILD in Japanese patients with SSc.

Clinical characteristics of our patient cohort were consistent with previous reports (Gabrielli et al. 2009; Broen et al. 2014; Nihtyanova et al. 2014), since patients with limited type had higher prevalence of anticentromere antibody and a lower frequency of internal organ involvement compared with patients with diffuse type (Table 1 and Fig. 1b). However, the ratio of limited type to diffuse type (116/23, 5.0) was higher than that in previous studies (Hashimoto et al. 2011; Nihtyanova et al. 2014; Shirai et al. 2015). For example, the ratio was 1.7 (252/146) at the Royal Free Hospital in the UK (Nihtyanova et al. 2014), 2.1 (273/132) at Kitasato University in Japan (Hashimoto et al. 2011), and 2.9 (127/44) at Keio University in Japan (Shirai et al. 2015). In addition, the 10-year survival rate in our study (92.0%) was greater than that found in previous studies from Japan and Western countries (72.6%-88.0%) (Jacobsen et al. 2001; Czirjak et al. 2008; Hashimoto et al. 2011). The reason for these discrepancies remains unclear; however, the prevalence of limited type without internal organ involvement has been increasing in recent years (Ferri et al. 2014), which may have attributed to these differences.

In our study, the prevalence of ILD was 47.5% and the most common HRCT finding of ILD was non-specific interstitial pneumonia (Fig. 2a). Patients with ILD had a significantly higher rate of anti-topoisomerase I antibody and a decreased survival rate compared with patients without ILD (Table 2 and Fig. 2b). These findings were also consistent with previous reports (Hashimoto et al. 2011; Wells and Denton 2014). Moreover, AE-ILD occurred at a frequency of 9.4% (13/139) in our study. Previous papers showed that the 1-year frequency of acute exacerbation was 1.25%-3.3% and a lifetime incidence 7.2% in patients with connective tissue disease (Park et al. 2007; Suda et al. 2009).

When limited to Japanese patients with SSc, there are three case series concerning AE-ILD (Suda et al. 2009; Tachikawa et al. 2012; Ando et al. 2013). Suda et al. (2009) reported that none out of 13 patients showed AE-ILD during median follow-up of 6 years; however, Ando et al. (2013) showed that 3 out of 71 patients (4.2%) died of AE-ILD during 9.8 years of follow-up. Our study result showing that 6 out of 139 patients (4.3%) died of AE-ILD is consistent with the latter (Ando et al. 2013). The 1-year frequency of AE-ILD in patients with idiopathic pulmonary fibrosis (IPF) was reportedly 5%-15% (Ryerson et al. 2015). We cannot directly compare our SSc cohort and IPF cohort; however, our study suggests that the prevalence of AE-ILD in Japanese patients with SSc is not low.

The clinical characteristics of patients who developed AE-ILD showed a greater incidence of overlap with PM/DM, and multivariate analysis indicated that an overlap with PM/DM was the most significant predictive factor (Tables 3 and 4). Suda et al. (2009) suggested that advanced age was a risk factor for acute exacerbation in connective tissue disease-related ILD, but the age of onset was not an associated factor in our study (Table 4). About 10%-20% of patients with SSc had overlapping features with other rheumatic diseases (Kowal-Bielecka et al. 2009; Pakozdi et al. 2011). Pakozdi et al. (2011) reported that the most common connective tissue disease was PM/DM, followed by rheumatoid arthritis and Sjögren's syndrome. It is still controversial whether SSc overlap syndrome is a separate disease entity or should be included in the two disease subsets of limited and diffuse type. However, a recent study has clearly demonstrated that its clinical course was different from that of limited or diffuse type with respect to autoantibodies and disease progression (Moinzadeh et al. 2015). The prevalence of AE-ILD in SSc overlap syndrome was not mentioned in this previous study (Moinzadeh et al. 2015), but our study suggests that Japanese patients with SSc-myositis overlap syndrome have a high risk of AE-ILD.

With regard to the treatment for AE-ILD, there is no consensus concerning appropriate management (Mathai and Danoff 2016). Therefore, we treated AE-ILD patients by combination therapy with a high dose of PSL and other immunosuppressive agents, similar to the treatment of patients who developed acute exacerbation of IPF (Kondoh et al. 1993; Azuma et al. 2005). However, the mortality rate was extremely high (6/13, 46%), and thus a more appropriate therapeutic strategy is required.

This study has also several limitations: 1) this is a retrospective, observational study. Therefore, a large prospective cohort study is essential to confirm our findings; 2) our data did not include the modified Rodnan total skin thickness score, which is the most common technique for the measurement of skin involvement (Furst et al. 1998; Clements et al. 2000); 3) anti-RNA polymerase III antibody was examined only when patients had negative results for other autoantibodies; and 4) autoantibodies that can be

detected in patients with SSc overlap syndrome (e.g., anti-PM-Scl antibody, anti-Ku antibody, and anti-RuvBL1/2) could not be examined at our institute (Kaji et al. 2014). 5) Our conclusion would simply reflect that PM/DM-related ILD has a high risk of AE. But even if we exclude patients with SSc-myositis overlap syndrome, 10 out of 131 patients (7.6%) developed AE-ILD, which again means that AE-ILD is not rare in SSc patients.

In conclusion, our study results demonstrated that 9.4% of SSc patients developed AE-ILD during the disease course and that coexisting PM/DM was the most significant predictive factor for acute exacerbation. The prognosis of patients who developed AE-ILD remains extremely poor, therefore a novel therapeutic strategy is urgently required.

Conflict of Interest

The authors declare no conflict of interest.

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