

## ORIGINAL

# Clinical features and outcome of acute exacerbation of interstitial pneumonia associated with connective tissue disease.

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**Abstract :** Acute exacerbation (AE) of interstitial lung disease is reported to be developed in not only idiopathic pulmonary fibrosis but also connective tissue disease-associated interstitial pneumonia (CTD-IP). As the significance of AE of CTD-IP has not been so widely recognized, its clinical feature is not fully elucidated. In the present study, we investigated the incidence, clinical features and outcome of AE of CTD-IP. We retrospectively reviewed admitted cases in our department with medical record from 2011 to 2015. Among 155 patients with CTD-IP, 10 (6.5%) cases developed AE (6 rheumatoid arthritis, 2 polymyositis/dermatomyositis, 1 systemic lupus erythematosus, 1 Sjögren syndrome), and one died of AE within 30 days. Median survival time after the onset of AE was 169 days in all 10 patients. The treatment with immunosuppressant just before AE onset might improve the prognosis of AE. The median survival time after the onset of AE was significantly longer in patients showing good response to corticosteroid compared with those with poor response to corticosteroid (805 days and 45 days, respectively) ( $p < 0.05$ ), suggesting that there are some cases in CTD-IP, showing the good response to corticosteroid even when AE was complicated. *J. Med. Invest.* 63 : 294-299, August, 2016

**Keywords :** connective tissue disease, interstitial pneumonia, acute exacerbation

## INTRODUCTION

Acute exacerbation (AE) of idiopathic pulmonary fibrosis (IPF) has been increasingly recognized. Revised Japanese criteria for AE of IPF (AE-IPF) have been available in 2004 in Japan (1) and the international consensus criteria were published in 2007 (2). Recently, AE has also been shown to develop in interstitial pneumonias (IPs) other than IPF, such as idiopathic nonspecific interstitial pneumonia (NSIP) and connective tissue disease (CTD) associated interstitial pneumonia (CTD-IP) (3-7). Park *et al.* (6) have described that AE developed in four of 93 patients with CTD-IP and that all patients who experienced AE died. Suda *et al.* (7) reported that six of 83 CTD-IP patients developed AE and that five of six (83.3%) expired. These data suggest that AE can also occur in CTD-IP, and this condition is closely similar to that of IPF with poor prognosis. However, the cumulative reported number of CTD-IP patients with AE is small, and its clinical characteristics remain to be fully determined. In the present study, we investigated the incidence, clinical features and outcome of AE of CTD-IP in our department.

## PATIENTS AND METHODS

### Patients

We retrospectively reviewed 3432 patients (all Japanese) who admitted to our department from January 2011 to December 2015. There were 312 patients diagnosed with CTD according to the

established criteria (8-13). Among them, 155 had accompanied with IP that was diagnosed by radiological pattern on high-resolution computed tomography (HRCT) according to the ATS/ERS/JRS/ALAT statement (14). The surgical lung biopsy was not done in any patients. Fifty-six patients developed acute deterioration of respiratory condition, and 10 were diagnosed as AE of IP (AE-IP) according to the criteria described below. The statement on consent to participate in this study was obtained from patients by written informed consent forms, if applicable, or by the disclosure of information for participation. The study was performed in accordance with the Declaration of Helsinki and the study protocol was approved by the Institutional Review Board of Tokushima University Hospital.

### Definition of AE-IP

AE-IP was defined based on the criteria for AE-IPF proposed by the Japanese guidelines (1) or the IPF Clinical Research Network (2), with a slight modification for the adaptation to CTD-IP (7, 15) : 1) previous or concurrent diagnosis of underlying fibrotic IP ; 2) unexplained worsening or development of dyspnea within 30 days ; 3) HRCT scan with new bilateral ground-glass opacities and/or consolidation superimposed on a background reticular or honeycombing pattern ; 4) no evidence of pulmonary infection by negative respiratory culture and negative blood tests for potentially infectious pathogens (e.g. Cytomegalovirus, *Pneumocystis jirovecii*) ; and 5) exclusion of left heart failure, pulmonary embolism and alternative causes for acute lung injury. If aforementioned deterioration and progression takes more than 30 days, we defined it as 'IP progression'.

### Statistical analyses

Survival was estimated using the Kaplan-Meier method, and the difference was assessed via the Log-rank test. Cox proportional hazards regression analysis was used to identify significant variables

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predicting survival status. Variables selected via univariate test were evaluated using a multivariate Cox regression analysis.  $p < 0.05$  was deemed statistically significant. All statistical analyses were performed with EZR (Saitama Medical Centre, Jichi Medical University ; Kanda, 2012, version 1.32), which is a graphical user interface for R (The R Foundation for Statistical Computing, version 3.25) (16).

**RESULTS**

*The incidence of AE in CTD-IP patients*

There were 312 CTD patients who fulfilled the eligibility criteria and 155 (49.7%) had IP among them in this study. Of all CTD-IP patients, 56 (36.1%) were hospitalized due to acute deterioration of respiratory condition. The hospitalization cause was AE in ten patients (6.5%). Other causes of acute deterioration were respiratory infection (24 cases), IP progression (5 cases), pulmonary hypertension (PH) (4 cases), drug-induced pneumonia (4 cases), alveolar hemorrhage (3 cases), pulmonary embolism (2 cases), sepsis (2 cases), pneumothorax (1 case) and aortic dissection (1 case) (Figure 1). No cases experienced the relapse of AE.

*Clinical features of patients with AE of CTD-IP*

Table 1 shows the clinical characteristics of 10 patients with AE of CTD-IP. There were three female (30%) and the median age at the onset of AE was 73 years. The median period was 958 days from the diagnosis of IP to AE occurrence. Six (60%) were ex-smokers with 3.5-5 pack-years of smoking history. Patients with rheumatoid arthritis (RA) (6 cases), systemic lupus erythematosus (SLE)

(1 case) and Sjögren syndrome (SS) (1 case) had UIP pattern in HRCT. Two polymyositis (PM)/dermatomyositis (DM) patients had NSIP pattern in HRCT. All except one SS patient were treated with corticosteroid. Patients with RA (4 cases) were treated with the combination of corticosteroid and other drugs ; methotrexate, cyclosporine A (CsA), etanercept, salazosulfapyridine, bucillamine. One SLE patient was accompanied with PH and treated with sildenafil. The mean serum levels of IP biomarkers, LDH and KL-6, were elevated. The mean value of the partial pressure of arterial oxygen/fraction of inspired oxygen ratio was 149.4.

*Treatment and outcome of AE in CTD-IP patients*

The treatment and outcome of AE of CTD-IP is summarized in Table 2. All patients were treated with broad-spectrum antimicrobial agents and high dose corticosteroid. Six received steroid pulse therapy, intravenous bolus 1000 mg methylprednisolone (mPSL), and two received half pulse (500 mg mPSL) therapy once daily for 3 days, then followed by 1 mg/kg/day and 0.5-0.7 mg/kg/day of prednisolone (PSL) in 5 and 3 patients, respectively. The dose of PSL was increased to 1 mg/kg/day without pulse therapy in two patients. The response to initial corticosteroid therapy was evaluated within one week and immunosuppressant was added in two patients with poor response to corticosteroid. The indicated immunosuppressant was intravenously administered cyclophosphamide (IVCY) and tacrolimus (TAC) in one each patient. Two patients were increased the dose of CsA. Only two patients were managed with a ventilator during their clinical course. Median survival time after the onset of AE was 169 days in all 10 patients (Figure 2A). The median survival time after the onset of AE was significantly longer in patients treated with corticosteroid only com-

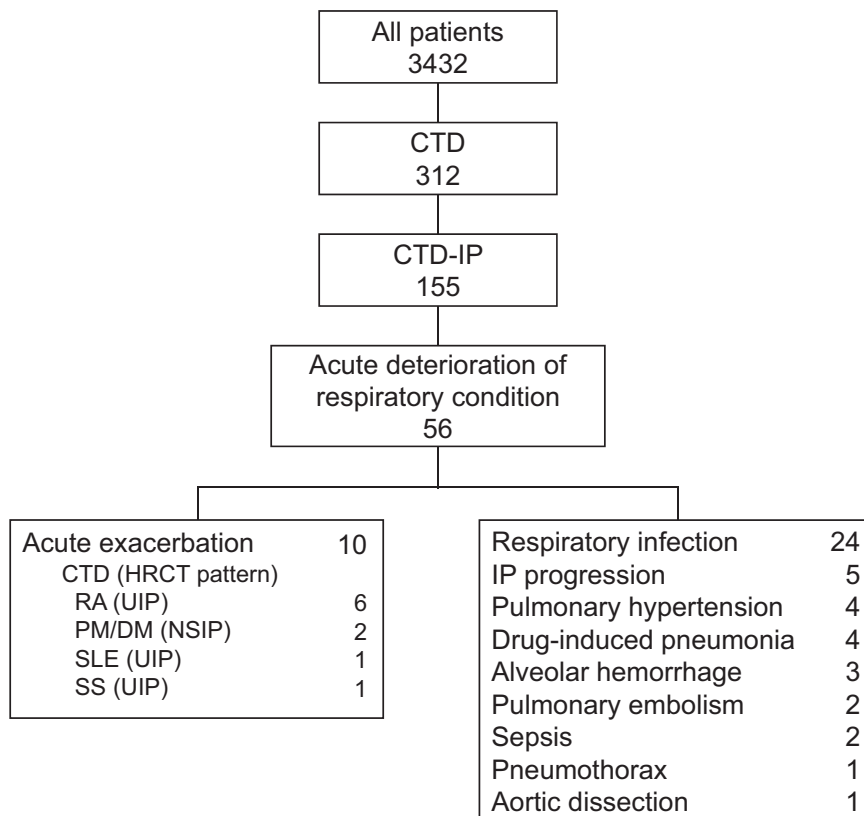


Figure 1. Trial profile. CTD ; connective tissue disease, IP ; interstitial pneumonia, HRCT ; high-resolution computed tomography, RA ; rheumatoid arthritis, PM ; polymyositis, DM ; dermatomyositis, SLE ; systemic lupus erythematosus, SS ; Sjögren syndrome, UIP ; usual interstitial pneumonia, NSIP ; nonspecific interstitial pneumonia

**Table 1.** Clinical characteristics of patients with AE of CTD-IP at the onset of AE

	Number of patients or values (N=10)
Sex male/female	7/3
Age (years) <sup>a</sup>	73 (61-83)
Smoking status current/ex-smoker/never	0/6/4
Period from diagnosis of IP to AE occurrence (days) <sup>a</sup>	958 (415-2714)
Underlying connective tissue disease	
RA	6
PM/DM	2
SLE	1
SS	1
Radiological pattern	
UIP	8
NSIP	2
Treatment for CTD and IP	
PSL only	3
PSL and other drugs <sup>b</sup>	6
No drugs	1
Long-term oxygen therapy	3
Laboratory data	
LDH (IU/mL) <sup>c</sup>	312.3±70.4
KL-6 (U/mL) <sup>c</sup>	955.7±455.4
PaO <sub>2</sub> / FIO <sub>2</sub> Ratio (N=7) <sup>c</sup>	149.4±100.5

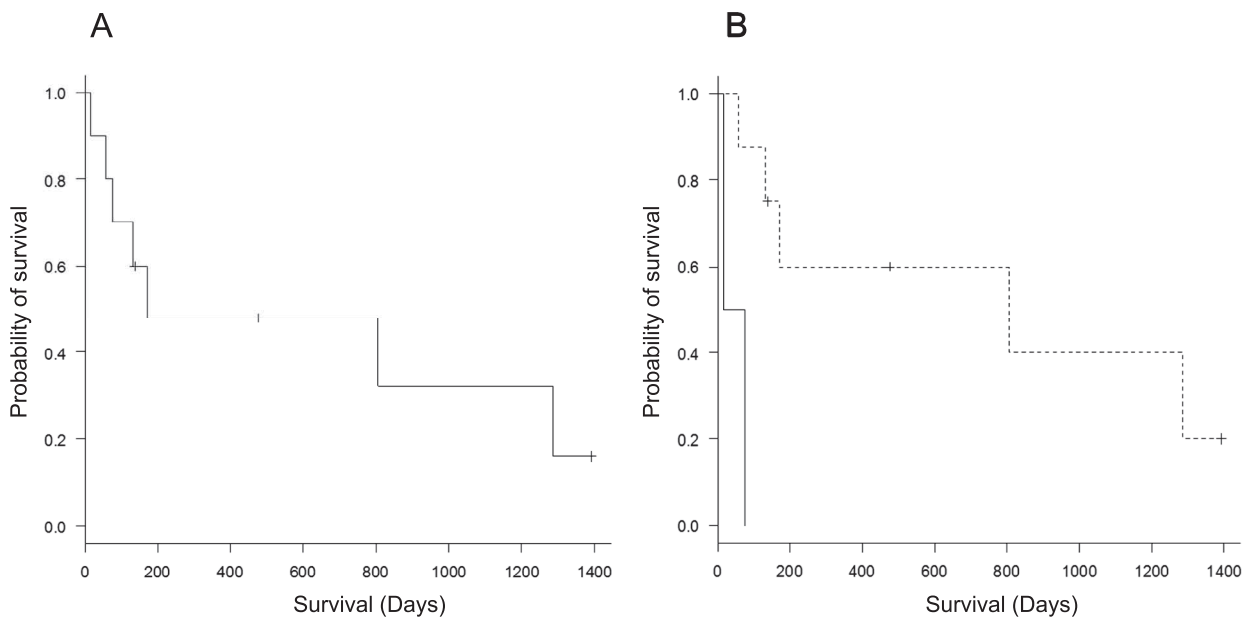
<sup>a</sup>; median (range), <sup>b</sup>; other drugs : methotrexate, cyclosporine A, etanercept, salazosulfapyridine, bucillamine, sildenafil. <sup>c</sup>; mean±SD  
 AE; acute exacerbation, CTD-IP; connective tissue disease associated interstitial pneumonia, RA; rheumatoid arthritis, PM; polymyositis, DM; dermatomyositis, SLE; systemic lupus erythematosus, SS; Sjögren syndrome, UIP; usual interstitial pneumonia, NSIP; nonspecific interstitial pneumonia, CTD; connective tissue disease, IP; interstitial pneumonia, PSL; prednisolone, LDH; lactate dehydrogenase, KL-6; Krebs von den Lungen-6

**Table 2.** Treatment and outcome of AE in CTD-IP patients

	Number of patients or values (N=10)
Treatment	
mPSL pulse therapy	
1 g/500 mg/none	6/2/2
PSL	
1 mg/kg/day/0.5-0.7 mg/kg/day	7/3
Immunosuppressants	
IVCY/TAC	1/1
Oxygen therapy	
Ventilation/NPPV/reservoir mask/nasal cannula	2/1/2/5
Outcome	
Died of AE	1 (10%)
Survive from AE	9 (90%)
Survival after AE (days) <sup>a</sup>	169 (15-1391)
Survival rate	
30 days	90% (9/10)
90 days	70% (7/10)
Causes of death	
AE	1 (10%)
Respiratory infection	2 (20%)
Others <sup>b</sup>	4 (40%)

<sup>a</sup>; median (range), <sup>b</sup>; Others : lung cancer, sudden death of unknown cause, aortic dissection, suffocation due to aspiration

AE; acute exacerbation, CTD-IP; connective tissue disease associated interstitial pneumonia, mPSL; methylprednisolone, PSL; prednisolone, IVCY; intravenous cyclophosphamide, CsA; cyclosporineA, TAC; tacrolimus, NPPV; noninvasive positive pressure ventilation



**Figure 2.** Kaplan-Meier estimates of the survival after the onset of AE of CTD-IP in all patients (A), and in patients with poor response to corticosteroid (straight line) or patients treated with corticosteroid only (dotted line) for the treatment of AE (B). *P* value was examined by the Log-rank test.

pared with those with poor response to corticosteroid (805 days and 45 days, respectively) ( $p < 0.05$ ; Figure 2B). Three patients died within 90 days; one patient, RA with UIP pattern, died of AE within 30 days, and the other two patients died of respiratory infection within 90 days. During follow-up periods, one each patient died of lung cancer, sudden death of unknown cause, aortic dissection, suffocation due to aspiration.

## DISCUSSION

AE of interstitial lung disease (ILD) is well known to be a fatal event during its clinical course. Contrary to AE-IPF, the significance of AE of CTD-IP has not been so widely recognized, and its clinical feature is not fully elucidated. In this study, we retrospectively investigated the clinical features and outcome of AE of CTD-IP. The number of CTD-IP patients was 155; 36.1% of all hospitalized CTD patients. Ten patients of CTD-IP (6.5%) were hospitalized due to AE, and the mortality of AE in patients experienced AE of CTD-IP was 10% (1/10). Median survival time after the onset of AE was 169 days in all 10 patients.

The incidence of IP associated with CTD is reported to be varied depending on the underlying CTD. In this study, it comprehensively was 36.1% and relatively higher, because the subject of this study was only hospitalized patients, especially hospitalized due to deterioration of respiratory condition. Generally, there are more female patients than male patients in CTD, but the ratio of male patients was relatively higher in our study, which is consistent with previous reports (6, 7, 15, 17). In RA-IP, Restrepo *et al.* (18) reported that 21% of RA patients was male, but 49% of RA-IP patients was male, and also that 72% of RA-IP patients had a smoking history. These mean that there are more male patients in CTD with IP patients. Smoking may relate to CTD-IP, similar to IPF.

The incidence of AE in IP remains mostly unknown. Recently, several studies reported that the 1-year incidence of AE was 14.2% in IPF (19), 4.2% in NSIP (6), and 1.25-3.3% in CTD-IP (6, 7). The incidence of AE in CTD-IP seems to be lower than that in IPF. Suda *et al.* (7) revealed an overall incidence of 7.2% in CTD-IP during follow-up periods, which was comparable with our findings in this study. The reported mortality of AE was above 70% in IPF (15, 20, 21), 34% in NSIP (15), and that in CTD-IP varied from 33% to 100% (6, 7, 15).

The poor prognosis of IP associated with RA have been reported (22). Similar to the previous studies (6, 7, 15), RA was the most common underlying disease which developed AE in this study (Table 3). AE also developed in SS-IP and SLE-IP. Parambil *et al.* (23) reported that three patients developed AE to die, among 18 patients with SS-IP (16.6%). And Lian *et al.* (24) reviewed 4038 SLE patients and described that 9.4% of SLE patients associated IP and 1.1% of SLE-IP developed AE. This shows that AE may develop in

also SS-IP or SLE-IP. The prognosis and response to corticosteroid is different between the underlying CTDs. Especially, a rapid progressive IP accompanied with PM/DM is corticosteroid resistant and very poor prognosis (25). The survival rate of AE in this study was 90%, which was better output among those studies. The precise reasons of better outcome are not clear. However, the rate of underlying CTDs such as RA and PM/DM might affect the prognosis of patients with AE in those reports. In addition, as an initial characteristics of the study population, immunosuppressant was used in 22% of patients in Suda's study (7), in 80% of patients in Tachikawa's study (15), and the combination therapy of PSL and other drug (immunosuppressant *et al.*) was used in 60% of patients in this study (Table 1). The survival rate of each study was 17%, 67%, and 90% respectively (Table 3). This suggests that the use of immunosuppressant just before AE may relate to good prognosis during the clinical course after AE.

For the treatment of AE-IPF, high dose corticosteroid is usually indicated according to the international guidelines and based on expert opinion (weak positive recommendation), while there is no recommendation regarding type, dose and duration of corticosteroids (14). Immunosuppressant can be combined with corticosteroid, yet without clear evidence of efficacy. Immunosuppressant indicated for the treatment of AE-IPF generally consists in IVCY (26), CsA or TAC. Some studies have shown that CsA and TAC improved the outcome of AE-IPF and that they prevented the relapse of AE (27-30). The AE of CTD-IP is managed according to the AE-IPF, with high-dose corticosteroid and immunosuppressant. The additional use of immunosuppressant with corticosteroid is thought to be effective for AE and to decrease adverse effects of corticosteroid. But, even though a few cases in this study, the patients with good response to corticosteroid significantly survived. These results suggest that there are some cases in CTD-IP, showing the good response to corticosteroid even when AE was complicated. Taken together with our observations and the clinical course of the previous studies (7, 27, 30), the prognosis of patients with AE-IP who did not respond well to corticosteroid is extremely poor, suggesting the significance of corticosteroid therapy in acute phase of AE. Otherwise, if a drug-induced pneumonia causes a respiratory deterioration, the prognosis may be good, and its differential diagnosis is difficult.

Several limitations in the present study should be noted. First, this was a retrospective study with small number of CTD-IP patients experienced AE. Therefore, there is a possibility that our findings may not be clinically relevant. While, the additional use of immunosuppressant revealed to be a significant poor prognostic factor in this study, there is a possibility that only the patients in inherently worse condition happened to be added immunosuppressant. Moreover, important parameters could have been missed in this analysis. Second, this study was conducted in a single institution, which could limit the generalizability of the findings.

Table 3. The incidence of CTD in AE of CTD-IP patients and outcome

Study (ref)	No. of CTD-IP	No. of AE (%)	No. of patients (No. of survivors from AE)				Survival (%)	
			RA	PM/DM	SLE	SS		SSc
Park <i>et al.</i> (6)	93	4 (4.3)	3 (0)	0	0	0	1 (0)	0
Suda <i>et al.</i> (7)	83	6 (7.2)	5 (1)	0	0	1 (0)	0	17
Tachikawa <i>et al.</i> (15)	ND	15	6 (5)	6 (3)	0	0	3 (2)	67 <sup>a</sup>
Toyoda (this study)	155	10 (6.5)	6 (5)	2 (2)	1 (1)	1 (1)	0	90

ND ; no data, CTD ; connective tissue disease, AE ; acute exacerbation, CTD-IP ; connective tissue disease associated interstitial pneumonia, RA ; rheumatoid arthritis, PM ; polymyositis, DM ; dermatomyositis, SLE ; systemic lupus erythematosus, SS ; Sjögren syndrome, SSc ; Systemic sclerosis

<sup>a</sup> ; The rate of 90-day survived patients

Further research on this topic should be performed involving multiple medical institutions. Despite these limitations, the present study provided useful information regarding the clinical features and outcome of AE of CTD-IP.

In conclusion, the incidence of AE in CTD-IP in this study was 6.5%, which was comparable with previous findings, but the mortality was 10%, which was relatively better. The treatment with immunosuppressant for CTD and CTD-IP before AE onset might improve the prognosis of AE of CTD-IP. Meanwhile, only the additional use of immunosuppressant revealed to be a significant poor prognostic factor, indicating the significance of corticosteroid therapy in acute phase of AE.

## CONFLICT OF INTEREST (COI)

The authors have no conflicts of interest to declare.

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