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Original article

Comparison between cryptogenic organizing pneumonia and connective tissue disease-related organizing pneumonia

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Abstract

Objective: Although the overall prognosis of CTD-related interstitial pneumonia is better than that of idiopathic interstitial pneumonia, the prognosis of CTD-related organizing pneumonia (CTD-OP) was suggested to be worse than that of cryptogenic organizing pneumonia (COP). The aim of this study was to compare the clinical features and outcome of the two conditions.

Methods: A retrospective review of 100 patients diagnosed by lung biopsy as having organizing pneumonia patterns (CTD, 24; COP, 76) at three tertiary referral centres.

Results: Underlying CTDs were mostly RA, SS and PM/DM. The median follow-up period was 43.6 months. There were no differences in initial symptoms, lung function or bronchoalveolar lavage fluid findings except significantly more females (83.3 *vs* 59.2%, $P = 0.048$) in the CTD-OP than in the COP group. Over 80% of the patients in both the groups improved. However, complete recovery rate was lower in CTD-OP (20.8%) than in COP (46.1%; $P = 0.028$) with a tendency towards higher recurrence rate in CTD-OP (40.0 *vs* 20.3%; $P = 0.072$). There was no significant difference in the frequency of rapid progression or overall survival between the two groups.

Conclusions: The clinical features and prognosis of CTD-OP are similar to COP. However, lower complete recovery rate with a tendency towards higher recurrence rate in CTD-OP compared with COP suggest the need for closer follow-up in patients with CTD-OP.

Key words: Cryptogenic organizing pneumonia, Connective tissue disease, Organizing pneumonia, Clinical features, Prognosis, Interstitial pneumonia, Rheumatoid arthritis.

CLINICAL SCIENCE

Introduction

All histopathological patterns of idiopathic interstitial pneumonia (IIP), including usual interstitial pneumonia (UIP), non-specific interstitial pneumonia (NSIP), diffuse alveolar damage (DAD) and organizing pneumonia (OP), have been reported in patients with CTD [1, 2]. Many studies showed that the patients with CTD-IP had a better overall prognosis than the patients with IIP [3, 4]. Since the prognosis of IIP is different according to specific histopathological patterns, it is important to compare the prognosis of CTD-IP patients that had the same histopathological pattern. Our recent study revealed that the prognosis of CTD-UIP was better than the prognosis of IPF/UIP, whereas the patients with idiopathic NSIP and CTD-NSIP had a similar prognosis [5]. Among the IIPs, cryptogenic OP (COP) has much better prognosis than other types of IIP. Most patients with COP recover either spontaneously or after treatment, although some patients show disease recurrence or relapse after discontinuation of treatment or reduction in drug dosage [6, 7]. In some rare cases, rapid progression has also been reported [8]. OP has also been seen in patients with CTD and it has

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been suggested that the prognosis of CTD-OP seemed to be poorer compared with the good prognosis of its idiopathic counterpart, COP [9–14]. Some reports have suggested that patients with underlying CTD are more likely to have a persistent and often progressive course compared with those with COP [15–17]. However, the number of subjects in those studies was too small to make a definite conclusion. The aim of this study was to determine whether the clinical features, course of disease and disease outcomes differ between patients with CTD-OP and those with COP.

Methods

Study populations

We identified 100 patients (COP, 76; CTD-OP, 24) from medical records at three university-affiliated hospitals between January 1995 and May 2009. All the patients had an OP pattern on lung biopsy with compatible clinical and radiological features. Patients with a history of drug, occupational or other environmental exposure known to cause interstitial lung diseases (ILDs) were excluded. Although this was a retrospective study, a thorough systematic history (see supplementary table 1, available as supplementary data at *Rheumatology* Online), physical examination and serological tests for CTD (ANA: $n = 93$, RF: $n = 91$, CCP: $n = 6$, SSA: $n = 80$) with frequent rheumatologic consultation were performed in most of the patients. Underlying CTDs were diagnosed according to the following criteria: the revised criteria of the ACR for RA [18], Bohan and Peter's criteria for PM/DM [19, 20], the revised international classification criteria for SS [21], diagnostic criteria previously described for MCTD [22] and criteria described by Chuang *et al.* [23] for PMR. Diagnostic histopathological specimens were obtained from surgical lung biopsies (COP: 75%, CTD-OP: 62.5%), transbronchial lung biopsies (COP: 22.4%, CTD-OP: 37.5%) or percutaneous needle biopsies (COP: 2.6%). In the cases for which surgical lung biopsy was not performed, only the patients with an adequate amount of tissue for the diagnosis of OP obtained by transbronchial lung biopsy or percutaneous needle biopsy, typical high-resolution computerized tomography (HRCT) findings (performed in all patients) and the clinical features were included. Typical HRCT findings of OP are diffuse or multifocal patchy bilateral ground glass opacity and/or consolidation without extensive reticulation or honeycombing [24, 25]. The diagnosis of all the patients was made by a multidisciplinary approach of experienced clinician, radiologist and pathologist. The study was approved by the Institutional Review Board of the Asan Medical Centre. Since this was a retrospective observational study, the written consent of the individual patients was waived.

Methods

All clinical data and laboratory results were collected from medical records. Lung functions were measured within 1 month of the lung biopsy. The results of these tests were expressed as percentages of the normal predicted values. All the pathological slides and images of HRCT, including follow-up films, were reviewed again by S.J.J. and M.-Y.K.

Majority of the patients had serial lung function tests and chest radiography during follow-up and HRCT at the end of therapy. Survival status was obtained from medical records, telephone interviews and/or the record of National Health Insurance of Korea.

Definitions of clinical course

Improvement was defined as a >10% increase in forced vital capacity (FVC), an increase of >15% in diffusing capacity for carbon monoxide (DL_{co}) and/or a >10% increase in total lung capacity (TLC) [26]. Normal or near normal lung function test and radiological findings at follow-up without relapse or recurrence were defined as complete recovery. Recurrence was defined as the appearance of characteristic new infiltrates on chest imaging and also with compatible clinical symptoms of the disease, after the cessation of treatment. Progression was defined as a >10% decrease in FVC, a >15% decrease in DL_{co} and/or a >10% decrease in TLC [26] despite treatment during the follow-up clinical visits. Rapid progression was defined as rapid onset of symptoms usually within 1 month before admission and a continuous, rapid aggravation of clinical and radiographic features despite treatment with high doses of steroids [17].

Statistical analysis

Data are presented as means ± S.D.s. Continuous variables were compared using the unpaired *t*-test or the Mann–Whitney *U*-test. Categorical variables were compared using the chi-square test or Fisher's exact test. Cumulative survival probabilities were estimated using Kaplan–Meyer survival curves and compared using the log-rank test. Cox's proportional hazards regression analysis was used to identify significant variables predicting survival. $P < 0.05$ was considered statistically significant. Statistical analyses were performed using SPSS version 14.0 (SPSS, Inc., Chicago, IL, USA).

Results

Baseline characteristics of CTD-OP and COP patients

The mean age of the study population was 55.7 years, and 35% of patients were male. The median follow-up duration for all patients was 43.6 months. The underlying types of CTD are shown in Table 1. The CTD-OP group had a higher proportion of females (83.3 *vs* 59.2%, $P = 0.048$; Table 2). There was a tendency towards higher CRP level in CTD-OP compared with the COP group. Otherwise, there were no significant differences between the two groups of patients in lung function,

PaO_2/fraction of oxygen (PaO_2/FiO_2) ratio in inspired air, or bronchoalveolar lavage (BAL) fluid findings.

Treatment

Most of the patients were treated with prednisolone, either alone or with cytotoxic agents; there were no differences in the initial dose of prednisolone, or duration of treatment between the two groups. Three patients with COP who presented with mild disease were not treated with prednisolone (Table 3). One additional patient, who was HCV positive, was not treated initially. However, the disease worsened during follow-up and prednisolone treatment was started.

Table 1 Underlying CTDs

Disease	Total	CTD first	ILD first	Concomitant
RA	7	4		3
SS	6		2	4
PM/DM	6			6
Overlap syndrome	3		1	2
PMR	1	1		
MCTD	1			1

Data are presented as number.

Clinical course and outcomes

After the initial treatment, most patients improved. However, the complete recovery rate was lower in CTD-OP (20.8%) compared with COP (46.1%; $P = 0.028$; Table 4). Although statistically insignificant, the recurrence rate tended to be higher in CTD-OP cases (40.0% of the patients who had improved initially) than in COP cases (20.3%; $P = 0.072$). There was no difference in the frequency of rapid progression (Table 4). Rapid progression developed in five (6.6%) COP patients and one (4.2%) CTD-OP patient, and all died from respiratory failure despite steroid pulse therapy with/without cytotoxic agent. We specifically looked for the evidence of underlying fibrotic disease, such as honeycombing in addition to newly developed ground glass opacity or consolidation in these patients; however, none of the patients had honeycombing on HRCT. During follow-up assessments, 20 (26.3%) patients with COP died from various causes including: disease progression ($n = 11$, 14.5%), malignancy ($n = 2$), chronic renal failure ($n = 1$) and suicide ($n = 1$), unknown causes ($n = 5$), and 3 (12.5%) patients with CTD-OP died due to disease progression. There were no significant differences in survival rate or in the median survival period between the two groups (Table 4).

Serial lung function change

The magnitude of the improvement in FVC and DL_{CO} at 12 months tended to be greater in the COP group than

Table 2 Comparison of the baseline characteristics between patients with CTD-OP and those with COP

Characteristics	CTD-OP	COP	*P*-value
Patients, *n*	24	76	
Age, years	54.8 ± 12.3	56.0 ± 11.5	0.669
Gender : female	20 (83.3)	45 (59.2)	0.048
Smoking (never : ex. : current)	66.7 : 29.2 : 4.2	76.3 : 13.2 : 10.5	0.827
Follow-up period, median (interquartile range), months	46.0 (13.9–58.7)	38.2 (13.0–68.6)	0.961
Dyspnoea	22 (91.7)	63 (82.9)	0.512
MRC grade (0–5)	2.6 ± 1.1	2.8 ± 1.0	0.310
CRP, mg/dl	4.9 ± 5.5	2.8 ± 4.7	0.107
PaO_2/FiO_2	341 ± 104	360 ± 91	0.425
ANA ($n = 24/69$)	17 (70.8)	22 (31.9)	0.001
RF ($n = 24/67$)	12 (50.0)	10 (14.9)	0.002
BAL, %	($n = 11$)	($n = 43$)	
Macrophages	49.8 ± 20.9	41.2 ± 22.3	0.192
Lymphocytes	34.7 ± 22.9	43.1 ± 22.9	0.273
Neutrophils	9.4 ± 9.9	11.1 ± 12.8	0.526
CD4/CD8 T-cell ratio	0.9 ± 1.2	0.6 ± 0.6	0.866
PFT, % pred.			
FVC	63.4 ± 17.9 ($n = 21$)	60.9 ± 17.0 ($n = 70$)	0.591
DL_{CO}	60.9 ± 20.6 ($n = 17$)	57.2 ± 18.7 ($n = 64$)	0.505
TLC	75.3 ± 20.4 ($n = 11$)	70.3 ± 14.6 ($n = 57$)	0.368
FEV_1	71.6 ± 17.0 ($n = 21$)	68.2 ± 18.9 ($n = 70$)	0.373

Data are presented as mean ± SD or *n* (%), unless otherwise indicated. MRC: Medical Research Council (MRC) dyspnoea scale; PFT: pulmonary function test; FEV_1: forced expiratory volume in 1 s.

Table 3 Comparison of the treatment regimen between patients with CTD-OP and those with COP

Treatment	CTD-OP	COP	*P*-value
Treatment regimen, *n* (%)			0.687
No treatment	0	3 (3.9)	
Prednisolone	12 (50.0)	36 (47.4)	
Prednisolone + cytotoxic agent	12 (50.0)	37 (48.7)	
Initial dose of prednisolone, mg/day	56.8 ± 24.4	54.6 ± 12.6	0.830
Steroid pulse, *n* (%)	2 (8.3)	5 (6.9)	1.000
Duration of treatment, months[a]	8.9 (4.9–15.2)	10.5 (4.0–14.7)	0.874

Data are presented as mean ± S.D. or *n* (%), unless otherwise indicated. [a]Median (interquartile range).

Table 4 Comparison of the clinical outcomes between patients with CTD-OP and those with COP

Outcomes	CTD-OP	COP	*P*-value
Improvement	20 (83.3)	69 (90.8)	0.309
Complete recovery	5 (20.8)	35 (46.1)	0.028
Recurrence[a]	8 (40.0)	14 (20.3)	0.072
Progression	3 (12.5)	5 (6.6)	0.394
Rapid progression	1 (4.2)	5 (6.6)	1.000
Stable	1 (4.2)	2 (2.6)	0.565
Overall death	3 (12.5)	20 (26.3)	0.265
Disease-related death	3 (12.5)	11 (14.5)	0.253
Survival, mean (95% CI), months	117.1 (95.6–138.6)	97.6 (82.9–112.4)	0.214
Mortality			
1 year	2 (8.7)	6 (8.1)	0.214
3 years	2 (8.7)	8 (11.6)	
5 years	3 (18.9)	11 (19.3)	

Data are presented as mean (S.D.) or *n* (%), unless otherwise indicated. Improvement was defined as two or more of the following: (i) an improvement of symptoms; (ii) reduction of parenchymal abnormalities on radiographic finding; (iii) physiological improvement defined by two or more of the following: (a) a >10% increase in FVC, (b) a 15% increase in DL_{co} and/or a >10% increase in TLC. Complete recovery: normal or near normal clinical and lung function test and radiological findings without relapse or recurrence. Recurrence: the appearance of characteristic new infiltrates on chest imaging with compatible clinical features after the cessation of treatment. [a]Percentage of the patients who had improved initially. Pd: prednisolone.

in the CTD-OP group (FVC: $P = 0.153$, DL_{co}: $P = 0.077$) (see supplementary table 2, available as supplementary data at *Rheumatology* Online).

Prognostic factors predicting clinical outcome in patients with OP

On univariate Cox's proportional analysis (Table 5), the dyspnoea score and lower PaO_2/FiO_2 ratios were found to be significant prognostic markers for mortality; however, the presence of CTD did not have prognostic value (Table 5). On multivariate analysis, only dyspnoea score was an independent prognostic factor for mortality.

Discussion

Our study showed that the majority of the patients in both groups improved after the treatment; however, approximately half of the patients with COP recovered completely in contrast to 21% in the CTD-OP group. There was a tendency towards more recurrence and lower magnitude of the improvement in lung function at 12 months in CTD-OP compared with the patients with COP; however, these findings were not statistically significant. Furthermore, the mortality rate and the frequency of rapid progression did not significantly differ between the two groups.

OP has been found in various CTDs, including RA, SLE, PM/DM, PMR and SS [11, 14, 16, 29, 30]. The reported frequency of OP in various CTDs was highly variable depending on the kind of CTD, the study population and the experimental design. For example, among five Japanese patients with CTD-OP, four had RA [29]. Tazelaar *et al.* [31] reported that 6 out of 15 patients with ILD associated with PM/DM had OP, whereas

Table 5 Prognostic factors for survival in patients with OP pattern using a Cox regression model

Parameter	Hazards ratio (95% CI)	*P*-value
Univariate analysis		
Age	1.025 (0.979–1.074)	0.293
Male	1.799 (0.629–5.144)	0.274
Ever-smokers	0.445 (0.099–1.987)	0.289
Presence of CTD	0.877 (0.244–3.150)	0.841
Dyspnoea score	2.662 (1.532–4.628)	0.001
CRP	1.042 (0.936–1.161)	0.452
PaO_2/FiO_2	0.990 (0.982–0.988)	0.019
FVC, initial (% predict)	1.012 (0.978–1.046)	0.507
DL_{co}, initial	0.987 (0.954–1.021)	0.453
TLC, initial	1.002 (0.952–1.054)	0.944
BAL, macrophages, %	0.986 (0.950–1.024)	0.470
Lymphocyte, %	1.019 (0.987–1.052)	0.248
Neutrophil, %	0.963 (0.882–1.053)	0.413
CD_4/CD_8	1.570 (0.759–3.246)	0.224
Rapid progression	1.000 (0.013–75.481)	1.000
Relapse	2.445 (0.763–7.837)	0.132
Recurrence	0.486 (0.109–2.176)	0.345
Multivariate analysis		
Dyspnoea score	3.112 (1.507–6.426)	0.002

in other papers, the OP pattern was found in 1 out of 22 patients with PM/DM who underwent surgical lung biopsies [11]. In our study, RA, SS and PM/DM were the predominant types of CTD. However, our study was not designed for this purpose and a large cohort study with proper design is needed to determine the dominant type of CTD in OP patients.

There was no significant difference in the clinical features observed between COP and CTD-OP patients, except an increased proportion of female and higher frequency of autoantibodies in the CTD-OP group, as expected. Also, the patients with CTD-OP had a tendency to have higher levels of CRP, suggesting the importance of an inflammatory process in the underlying CTD. However, a significant proportion of the patients with COP also had positive ANA and elevated CRP level.

Although OP is a well-known lung manifestation in patients with CTD, the clinical outcome of CTD-OP has not been well defined. The overall prognosis of interstitial pneumonia related to CTD was better than IIP and also the prognosis of CTD-UIP was reported to be better than IPF/UIP [3–5]; however, there was a suggestion that the prognosis of CTD-OP may be worse than that of COP [15, 17]. In the paper by Epler *et al*. [15], all five patients with OP related to CTD deteriorated, and none of these patients completely recovered. Cohen *et al*. [17] reported findings from 10 patients with rapidly progressive OP. Of these 10 patients, all three with CTD (RA or DM) died, suggesting a poor prognosis of CTD-OP [17]. In contrast to these studies, Yousem *et al*. [28] reported that none of the six patients with OP and RA developed a progressive lung disease. In the paper by Yamamoto *et al*. [29], all five patients with CTD-OP recovered, and only one patient experienced a relapse. However, the number of patients in these studies was too small to make generalizations about the clinical course of CTD-OP. Our study included 100 patients with OP, who were followed up for enough periods and confirmed that the overall prognosis was good in both groups (improvement in >80%). Almost half of the patients with COP recovered to normal state, whereas this complete recovery rate was lower in CTD-OP.

On the comparison of the serial lung function change between the COP and CTD-OP groups, there was a tendency towards higher magnitude of improvements in the COP group compared with the CTD-OP group; however, it was difficult to draw concrete conclusions because of the missing data of the follow-up lung function test.

In contrast to the study by Cohen *et al*. [17], which reported that the rapidly progressive form of OP was more frequent in patients with underlying CTD, the proportion of patients with a rapidly progressive form of disease in our study was similar. Since our study included only biopsy-proven OP cases, patients with a rapidly progressive form of OP who were too sick to undergo biopsy might not be included.

After the cessation of therapy, there was a tendency towards higher recurrence in patients with CTD-OP compared with COP; however, the difference was not statistically significant. Lohr *et al*. [27], in their study of 74 patients with OP (COP, 37; second OP, 27 including 10 with CTD; focal OP, 10), also reported that recurrence was more frequent (17.3%) in patients with secondary OP compared with those with COP (12.9%). The recurrence rate in COP in that study was comparable to our COP patients (18.4%). Although the recurrence rate of CTD-OP was not specifically reported, their secondary OP included hematological malignancies and most of them were reported as died. If we can speculate that most of the recurrences ($n = 4$) might occur in the patients with CTD-OP ($n = 10$), then the recurrence rate of CTD-OP might be comparable to ours [6, 27]. Furthermore, there was no statistically significant difference in mortality rate between COP and CTD-OP in our study: either all-cause mortality or disease-related mortality.

On univariate analysis with Cox's proportional hazard model to evaluate the risk factors for mortality in the patients with OP, only dyspnoea score ($P = 0.001$) and a lower PaO_2/FiO_2 ratio ($P = 0.019$) were the significant predictive factors for mortality. The presence of CTD was not related to mortality confirming the similar prognosis between COP and CTD-OP.

Our study had several limitations. First, it was a retrospective study performed at three medical centres in Korea, and the treatment regimen and duration were not standardized. However, most of the patients were treated with prednisolone, either with or without cytotoxic agents in similar dosage, and there was no difference in the treatment regimen or duration of therapy between the COP and CTD-OP patients. Second, this study included only the patients with biopsy-proven OP; therefore, the

patients who were too sick to tolerate bronchoscopic or surgical lung biopsy might have been excluded. This could have affected the frequency of rapid progression and resulted in a failure to demonstrate the higher frequency of rapid progression in CTD-OP patients. However, without biopsy, we cannot differentiate OP and DAD pattern, which is a distinct subgroup of interstitial pneumonia with worse prognosis. Third, the number of patients with CTD-OP in our study was relatively small compared with COP. However, this is the largest series of CTD-OP and COP cases reported. Fourth, the median follow-up period was relatively short (44 months) with high variability (interquartile range 14–67 months) due to follow-up loss or variable survival period. Nevertheless, it was sufficient to reveal the course and final outcomes of OP, because the majority of the patients improved with a relatively low recurrence rate. The last but not the least limitation was for the possibility that some COP cases might actually have had CTD. As more RNA synthetases are identified, it has become apparent that a number of cases believed to have COP actually had myositis-associated OP. Further study with measurement of various anti-synthetase antibodies is required. As OP is very often an early feature of disease, or may precede systemic disease, it is also possible that the treatment might have prevented the development of CTD in some COP cases. However, many of our patients were followed up for a significant period after the cessation of steroid therapy and none of them developed a manifestation of CTD.

As a conclusion, our data suggest that the overall prognosis of both COP and CTD-OP was good with high response rate and low mortality rate. However, lower complete recovery rate with a tendency towards higher recurrence rate in CTD-OP compared with COP suggest the need for closer follow-up in patients with CTD-OP.

Rheumatology key messages

- Prognosis of COP and CTD-OP was good with high response rate and low mortality rate.
- CTD-OP had lower complete recovery rate with a tendency towards higher recurrence compared with COP.

Disclosure statement: The authors have declared no conflicts of interest.

Supplementary data

Supplementary data are available at *Rheumatology* Online.

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