Cicatricial organising pneumonia associated with fibrosing interstitial pneumonia – a clinicopathological study

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Aims: The recent recognition of cicatricial organising pneumonia (ciOP) indicates that the ciOP may resemble or simulate fibrotic interstitial pneumonia; however, there has been great uncertainty regarding the affected populations, pathogenesis, clinical relevance and

characteristics. In this study, we compared the characteristics of fibrotic interstitial pneumonia with and without ciOP.

Methods and results: We enrolled 121 patients from the consultation archive whose pathological findings were fibrotic interstitial pneumonia and for whom follow-up clinical data were available. We reviewed these cases histopathologically and classified them according to whether or not they showed ciOP. We compared the clinicopathological features between the two groups. CiOP, histopathologically characterised by deposition of dense collagenous fibres within the alveolar space without destruction of the lung structure, was found in 48 patients (39.7%). None of the cases with ciOP experienced acute exacerbation during 12 months' follow-up. The group with ciOP had more severe diffusion impairment but this, together with restrictive ventilatory impairment, improved significantly compared to the group without ciOP.

Conclusion: CiOP is a histopathological finding commonly found in fibrotic interstitial pneumonia. It does not relate to acute exacerbation or decrease in pulmonary function.

Introduction

Fibrosing interstitial pneumonia (IP), which is a chronic but progressive lung disease, is histopathologically characterised by proliferation of collagen fibres in the lung parenchyma. Fibrosing IP includes the following idiopathic or secondary lung diseases: idiopathic pulmonary fibrosis (IPF),[1] idiopathic non-specific interstitial pneumonia (NSIP),[1,,2] some cases of unclassifiable idiopathic IP mixed with usual interstitial pneumonia (UIP) or NSIP pattern,[1] fibrosing hypersensitivity pneumonitis (HP),[3] connective tissue disease associated interstitial lung disease (CTD-ILD),[4] drug-induced interstitial lung disease,[5] pneumoconiosis and others. Recently, it has been reported that nintedanib, which is an antifibrotic agent, inhibits the decline of lung function in patients with fibrosing IP showing progression of fibrotic changes, also known as progressive fibrosing interstitial lung disease (PF-ILD).[6] For pathologists, the

histological parameters of disease progression in fibrosing IP are important in considering the treatment strategies of patients. The fibroblastic focus in UIP cases[7–9] or the presence of UIP lesions in CTD-ILD cases[10,11] are known as histopathological indicators of progression; however, the histological prognostic factors for all fibrotic IPs are still unknown.

Organising pneumonia (OP) is characterised by histopathological findings of granulation tissue plugs within alveolar ducts, known as Masson bodies,[12] accompanied by oedema and loose fibrosis. OP is observed not only in idiopathic cases, called cryptogenic organising pneumonia (COP), but also in secondary cases including infection, connective tissue disease, hypersensitivity pneumonitis, drug toxicity and radiation therapy.[13,14] OP generally regresses with corticosteroid treatment, leaving little chronic fibrosis or architectural distortion. However, several recent studies have reported the presence of OP with chronic fibrotic changes or scarring.[15–19] These studies referred to such conditions as 'cicatricial variant of COP',[15–17] 'collagenised OP'[18] or 'fibrosing OP',[19] and they were reported as a subtype of COP. We have encountered similar cases in which fibrosis replaced OP within the alveolar space without architectural distortion, and it has been known in Japan for some time as 'scarred OP', which was not considered as a phenotype of the disease, but rather a histopathological finding. In our practice, this histopathological finding, cicatricial OP (ciOP), was seen not only in COP cases, but also as a component of the histopathological spectrum in fibrosing IP cases. The frequency and clinical relevance of ciOP in fibrosing IP are unknown. The mixture of OP and fibrosing IP suggests an acute exacerbation of fibrosing IP;[20,21] however, the mixture of ciOP and fibrosing IP may have a different prognosis. The objective of this study was to clarify these issues by comparing the characteristics of fibrosing IP with and without ciOP.

Materials and methods

STUDY SUBJECTS

This was a retrospective cohort study. From January 2016 to August 2018 there were 402 cases of surgical lung biopsy at the participating institutions, most of which were interstitial lung disease. Among these there were 231 cases with the histopathological pattern of fibrosing IP composed of dense collagenous fibrosis and, of these, 121 cases had available clinical follow-up data. Three pathologists reviewed these and divided them into two groups: fibrosing IP with and without ciOP. Consistent with previous publications,[15–19] ciOP was defined pathologically on the basis of chronic fibrotic changes composed of dense collagen fibres within the alveolar space of the lung, with no architectural destruction. Elastica van Gieson (EVG) staining revealed that the alveolar structure consisting of elastic fibre was mainly intact and that air spaces were filled with dense fibrosis, showing a red colour on EVG. This made it possible to recognise these lesions as ciOP, rather than the fibrosis associated with fibrotic IP and the collagen fibres found in normal structures (Figure 1). The presence of any degree of ciOP was considered positive. We further rated the extent of ciOP semi-quantitatively: score 3 is predominantly ciOP, score 2 is moderately developed ciOP, score 1 is minimal distribution of ciOP and score 0 is no ciOP (Supporting information).

The ciOP is a newly identified finding among fibrotic lung lesions. According to the histopathological definition outlined above, it is not similar to the ordinary OP. In the latter, Masson bodies served as a diagnostic feature representing an injury of subacute onset. For that reason, we considered ciOP as a superimposed finding on fibrotic IP rather than an exclusion criterion to the guideline diagnosis of UIP. Clinical background, diagnosis made by multidisciplinary discussion (MDD)[1] and results of blood and pulmonary function tests 6 or 12 months after surgical lung biopsy were compared between the two groups.

This study was conducted in accordance with the tenets of the Declaration of Helsinki and approved by the Institutional Review Board of our institute (Nagasaki University Hospital Clinical Research Ethics Committee, 16 October 2018, approval no. 18101503).

STATISTICAL ANALYSIS

All numerical data are presented as median values with 25–75% interquartile range. Statistical significance of the difference between the two groups was analysed using Wilcoxon's rank-sum test or Fisher's exact test. Multivariate analysis was performed using logistic regression, and factors were extracted using a backward–forward stepwise procedure. Statistical significance was defined as $P < 0.05$, and all statistical analyses were performed using JMP version 14.0 (SAS Institute, Cary, NC, USA). Additional Supporting information Tables and Figures are shown online.

Results

PATIENT CHARACTERISTICS

Information on all patients is presented in Table 1. Of the 121 patients, histopathological findings of ciOP were observed in 48 patients (39.7%). Between the ciOP-positive and ciOP-negative groups, there were no differences in age, sex, smoking history or antigen exposure. In blood test results, higher Krebs von Lunge-6 (KL-6) values were observed in the group with ciOP ($P = 0.030$). There was no significant difference in the frequencies of positive inflammatory markers, hypoxaemia, antinuclear antibodies or rheumatoid factor. Pulmonary function testing revealed that the group with ciOP had greater diffusion impairment ($P = 0.017$), but there was no significant difference in the severity of restrictive ventilatory impairment. Fractionation of bronchoalveolar lavage fluid (BALF) revealed a high lymphocyte fraction (10.8 versus 6.4%) in the group with ciOP ($P = 0.015$), which may indicate a lymphocytic infiltration around the ciOP.

Histopathologically, 70 of 121 cases showed a UIP pattern and 25 (35.7%) had ciOP. Of 35 cases with an NSIP pattern, 16 (45.7%) had ciOP. Twelve cases were determined as

unclassifiable IP and five (41.7%) had ciOP. In MDD, 61 of 121 cases were diagnosed with IPF and 18 (29.5%) had ciOP. Of 18 cases diagnosed by MDD with idiopathic NSIP, nine (50.0%) had ciOP. Finally, 23 cases were diagnosed with CTD-IP and 10 (43.5%) had ciOP. Four cases were diagnosed with HP and three (75.0%) had ciOP. Although the proportion of HP with ciOP was high, statistical significance could not be indicated due to the small number of cases. Eight (44.4%) of 18 unclassifiable idiopathic IP cases had ciOP. There was a slightly smaller frequency of idiopathic pulmonary fibrosis (IPF) diagnosis and a slightly greater frequency of non-specific interstitial pneumonia (NSIP) and unclassifiable interstitial pneumonia diagnoses in the group with ciOP, but there were no significant differences ($P = 0.144$).

None of the patients we reviewed in this study had a history of acute exacerbations prior to biopsy. In other words, there was no relationship between past history of acute exacerbation and the presence of ciOP.

HISTOPATHOLOGICAL FINDINGS

Surgical lung biopsy was performed at two locations, including the lower lobe of the lung in all cases. Each section was assessed by haematoxylin and eosin (H&E) staining and EVG staining. Seven of 48 cases (14.6%) showed ciOP as the predominant histological finding (score 3) but the cases purely composed of ciOP, identical to cicatricial organising pneumonia,[15–19] were not found in our series. Fifteen cases (31.3%) showed ciOP as a second major histological pattern (score 2) and 26 cases (54.2%) showed ciOP as a minor component of whole disease (score 1). Most cases showed dense fibrotic interstitial pneumonia, which was consistent with UIP or fibrotic NSIP mixed with ciOP (Figures 2–5). CiOP resembled other types of dense fibrotic interstitial pneumonia when only H&E staining was used. However, EVG staining revealed that the alveolar structure was mainly intact and that air spaces were

filled with dense fibrosis, making it possible to recognise these lesions as ciOP. CiOP could exist in any lobe of the lung; not only inside the alveoli, but also in the fibrotic changes (Supporting information, Figure S4).

In some cases, ciOP was observed focally in ordinary OP (Figure 6). There were numerous Masson bodies inside the alveoli and the presence of ciOP foci showing chronic fibrotic change, although not necessarily noticeable with H&E staining, was highlighted by EVG staining. These changes might illustrate the scarring process inside the OP lesions.

CLINICAL OUTCOMES

Forty-two cases were treated with corticosteroids and immunosuppressants such as tacrolimus after the diagnosis. Forty patients were treated with antifibrotic agents such as pirfenidone and nintedanib after the diagnosis. There was no difference in treatment regimens between the two study groups. Changes in blood and pulmonary function tests in the groups with and without ciOP 6 and 12 months after diagnosis are shown in Table 2. Carbon monoxide diffusion capacity was lower and KL-6 was higher at the time of diagnosis in the group with ciOP; however, their improvement was significantly greater compared to the group without ciOP (P = 0.022 and 0.043, respectively). Restrictive ventilatory impairment also showed significant improvement in the group with ciOP than in the group without ciOP (P = 0.001). None of the cases with ciOP experienced an acute exacerbation during a 1-year follow-up.

Patients' characteristics and clinical outcomes in IPF groups with and without ciOP are shown in the Supporting information Tables.

MULTIVARIATE ANALYSIS

The results of the multivariate analysis are presented in Table 3. Significant differences were observed in blood and pulmonary function tests, cell ratios within the bronchoalveolar lavage

fluid (BALF) and clinical course between the groups with and without ciOP using univariate analysis. Multivariate analysis of these items revealed that restrictive ventilatory impairment at 6 months after diagnosis was significantly reduced in the group with ciOP.

In the present study, we could not detect any significant differences in the patient characteristics or clinical courses among various intensities of ciOP.

SUBSET ANALYSIS IN THE IPF GROUP

We also performed a subset analysis limited to IPF patients (Supporting information Tables). Eighteen of 61 IPF patients (29.5%) showed ciOP histologically. There tended to be more smokers ($P = 0.036$), having higher KL-6 values ($P = 0.023$) and greater diffusion impairment ($P < 0.001$) in the group with ciOP. Restrictive ventilatory impairment showed improvement in the group with ciOP, in spite of greater diffusion impairment, but did not reach statistical significance ($P = 0.094$), probably due to the limited number of patients in this cohort.

Discussion

This study demonstrated that ciOP not only exists as a part of OP but is also included in fibrosing IP, which is a frequent histopathological finding (39.7%). Because some ciOP cases show more oedematous and myxoid variants, ciOP can be considered a sequel of conventional OP. It is important that none of 48 fibrosing IP with ciOP cases developed an acute exacerbation,[22,23] despite the inclusion of 18 IPF cases. When OP coexists with fibrosing IP acute exacerbation of fibrosing IP should be considered,[20,21] as acute exacerbation of fibrosing IP is one of the critical events that is strongly associated with rapid deterioration of respiratory status and mortality.[21,22,24,25] The risk of acute exacerbation of IPF, which has been reported to be 5–15% per year,[26,27] is higher than the risk associated with other types of fibrosing IP. As none of the cases with ciOP experienced acute exacerbation within a year, it appears that ciOP

is not predictive of acute exacerbation in fibrosing IP. Although it is uncertain why ciOP was inversely associated with the occurrence of acute exacerbation in our series, the pathogenesis of ciOP and that of acute exacerbation in fibrosing IP may be different.

With reference to the changes in pulmonary function tests and blood tests, multivariate analysis revealed a slight but significant improvement of restrictive ventilatory impairment after 6 months in the group with ciOP. While the magnitude of this change was relatively small, it is known that deterioration in forced vital capacity correlates with poor prognosis and is important in predicting disease progression.[28–30] Pulmonary function showed mild improvement over time in both groups, with and without ciOP, which was mainly due to effect of treatment in non-IPF cases. Moreover, the improvement was pronounced in the ciOP group ($P = 0.001$). Our findings indicate that ciOP may be a factor suggesting good prognosis in fibrosing IP. CiOP is fibrosis limited to the alveolar space, and consequently is not accompanied by structural distortion of the lung parenchyma, unlike UIP lesion, which may be the reason why the deterioration of lung function did not progress. Our findings may indicate that ciOP is a histopathological clue suggesting a favourable subtype of fibrosing IP.

A review of the pertinent literature showed that histological findings similar to the described above have been reported previously under different names. For example, cases enrolled into our study were diagnosed as ‘scarred OP’, a terminology informally adopted in Japan. Yousem described 12 cases in which the loose fibromyxoid connective tissue of OP displayed progressive fibrosis with formation of intraluminal dense eosinophilic scar tissue without destruction of the underlying lung architecture in COP patients, designated ‘cicatricial variant of cryptogenic organising pneumonia’.[15] Woge *et al*. found that the clinical and radiological course of patients with cicatricial variant of COP was indolent or favourable.[17] OP with hyalinised scarring was also described as ‘fibrosing OP’ by Beardsley *et al*.[19] In these reports, OP with hyalinised scarring was considered to be a subgroup of COP. However, the

present study showed that ciOP is not only a subgroup of COP, but also a histological finding that can be mixed in other histological pattern of IPs. Churg *et al*. reported that OP with hyalinised scarring could mimic fibrosing interstitial pneumonia such as UIP and could develop in patients positive for antinuclear antibodies or diagnosed with Ehlers–Danlos syndrome.[16] Mengoli *et al*. reported similar findings in three cases of colon cancer metastasising to the lung after chemotherapy, and reported these lesions as 'collagenised organising pneumonia'.[18] These reports suggest that many cases of ciOP may be diagnosed as fibrosing IP, including UIP, NSIP or secondary causes of interstitial pneumonia, such as drug-induced lung injury or chronic hypersensitivity pneumonitis. Given an existing variety of names probably describing the same entity (ciOP, cicatricial variant of OP, fibrosing OP, collagenised OP, scarred OP), there is a need to reach a consensus among experts and unify the terminology of ciOP.

In the present study, we reviewed fibrosing IP cases and examined the characteristics of the group containing ciOP. In addition, our series showed that ciOP not only mimics fibrosing IP, as Churg *et al*. reported,[16] but may also coexist as pathological findings mixed with fibrosing IP. The clinical significance is that ciOP may be a factor of good prognosis for fibrosing IP. An additional large-scale multi-institutional study is recommended to prove this hypothesis.

This study has some limitations. First, it was a retrospective cohort study, not prospective. Secondy, it did not include data on long-term prognosis; therefore, the prognosis of patients was estimated by their rate of decrease in pulmonary function, which is a common measure of disease control in interstitial lung disease. Further evaluation of additional endpoints, such as survival, is needed.

In conclusion, ciOP is characterised by deposition of dense collagenous fibres within the alveolar space without destruction of the lung structure. CiOP is commonly associated with

fibrosing IP, which has a low risk of acute exacerbation, and shows small improvement of restrictive ventilatory impairment.

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Conflicts of interest

The authors declare that no potential conflicts of interest exist with any company/organisation whose products or services are discussed in this article. The views expressed in the submitted article are our own and not an official position of the institution or funder.

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Figure 1. Histopathology of cicatricial organising pneumonia (ciOP). **A,B,** When ciOP is observed on haematoxylin and eosin (H&E) staining, it can be recognised as dense collagenous fibrosis in the alveoli (arrowhead). **C,D,** CiOP shows dense fibrotic changes inside the alveoli, highlighted red on Elastica van Gieson (EVG) staining, but the elastic fibres of the alveolar septum surrounding ciOP are maintained without architectural destruction.

Figure 2. Cicatricial organising pneumonia (ciOP) resembling usual interstitial pneumonia (UIP). **A,B,** In this specimen, paraseptal dense fibrosis of UIP is seen along with foci of ciOP. **C,D,** The area of ciOP is difficult to distinguish by haematoxylin and eosin (H&E), but Elastica van Gieson (EVG) staining highlights areas of UIP (blue arrowheads) and ciOP (yellow arrowheads), which maintain the lung structure and fill the airspace with dense collagenous fibres (yellow arrowhead). Contrastingly, the dense fibrosis of UIP (blue arrowheads) shows architectural destruction. **A,B,** H&E; **C,D,** EVG.

Figure 3. Cicatricial organising pneumonia (ciOP) seen in the background of probable usual interstitial pneumonia (UIP). **A,** Lower magnification image of the case in which UIP lesion was observed mixed with other fibrotic changes. **B,** Middle magnification image of the area framed by the blue square. **C,D,** High magnification image of the area framed by the yellow square and showing much ciOP (blue arrowheads). **A,B,C,** Haematoxylin and eosin (H&E); **D,** Elastica van Gieson (EVG).

Figure 4. Cicatricial organising pneumonia (ciOP) seen in the background of non-specific interstitial pneumonia (NSIP), looking very similar to NSIP-like fibrosis. **A,B,** Diffuse loose fibrosis, reminiscent of NSIP. **C,D,** Elastica van Gieson (EVG) staining revealed elastic fibres without destruction of the alveolar septum and dense collagen fibres inside the alveoli, indicating ciOP (arrowhead). **A,B,** Haematoxylin and eosin (H&E).

Figure 5. Cicatricial organising pneumonia (ciOP) mimicking non-specific interstitial pneumonia (NSIP). This case was diagnosed with NSIP pattern pathologically and idiopathic NSIP in multidisciplinary discussion (MDD). **A,** Lower magnification image of the case in which ciOP is predominant but resembled fibrotic NSIP. **B,** Middle magnification image of the

area framed by the blue square. CiOP was observed (blue arrowheads). **C,D,** Middle magnification image of the area framed by the yellow square and showing some ciOP (blue arrowheads). **A,B,C,** Haematoxylin and eosin (H&E); **D,** Elastica van Gieson (EVG).

Figure 6. Cicatricial organising pneumonia (ciOP) mixed with ordinary organising pneumonia (OP). This case was diagnosed with (NSIP) pattern pathologically, and autoimmune/inflammatory syndrome induced by adjuvants (human adjuvant disease) in multidisciplinary discussion (MDD). **A,B,** In this case, areas with ciOP (enclosed by yellow line) are surrounded by ordinary organising pneumonia (OP) and difficult to recognise by haematoxylin and eosin (H&E). **C,D,** Fibrotic lesions of ciOP consisting of dense collagenous fibres (arrowheads) show no destruction of the surrounding alveolar septa. **C,D,** Elastica van Gieson (EVG).

Table 1: Patients characteristics

	All patients	With ciOP	Without ciOP	P value
Number	121	48	73	
Age	64 (57-67)	62 (57-67)	64 (57-68)	n/a
Gender: Male	74 (61.2%)	32 (66.7%)	42 (57.5%)	n/a
Smoker	73 (60.3%)	33 (68.8%)	40 (54.8%)	n/a
Baseline blood data				
KL-6 (IU/mL)	1211 (713-2007)	1495 (894-2360)	1055 (675-1716)	0.030
LDH (IU/L)	221 (197-253)	226 (200-271)	217 (192-251)	n/a
CRP (mg/dL)	0.08 (0.04-0.24)	0.13 (0.04-0.32)	0.07 (0.03-0.23)	n/a
Specific antibody (positive patients number)				
RF > 30 IU/mL	17 (14.0%)	6 (12.5%)	11 (15.1%)	n/a
ANA ≧ 1:320	20 (16.5%)	11 (22.9%)	9 (12.3%)	n/a
Anti ARS antibody	9 (7.4%)	5 (10.4%)	4 (5.5%)	n/a
Pulmonary function test (%)				
%FVC	88.1 (69.9-102.9)	96.5 (69.2-112.7)	85.1 (70.4-99.1)	n/a
%DLCO	67.6 (55.1-81.0)	61.3 (51.3-73.8)	69.4 (59.7-83.5)	0.017
BALF analysis				
Total cell count (×10^5/mL)	1.74 (1.01-2.60)	1.78 (1.02-2.93)	1.69 (1.00-2.53)	n/a
Macrophage (%)	84.4 (66.1-92.0)	78.8 (46.8-90.0)	87.2 (69.1-93.8)	0.013
Lymphocyte (%)	8.0 (3.6-20.7)	10.8 (4.4-33.2)	6.4 (3.4-10.4)	0.015
MDD diagnosis				n/a
IPF	61 (50.4%)	18 (37.5%)	43 (58.9%)	
NSIP	18 (14.9%)	9 (18.8%)	9 (12.3%)	
CTD-ILD	23 (19.0%)	10 (20.8%)	13 (17.8%)	
CHP	4 (3.3%)	3 (6.3%)	1 (1.4%)	
UCIP	13 (10.7%)	8 (16.7%)	5 (6.8%)	
Others**	2 (1.7%)	0 (0%)	2 (2.7%)	
Histological findings				
CiOP (score 1/2/3)*		26/15/7		
Histological diagnosis				
UIP pattern	70 (57.9%)	25 (52.1%)	45 (61.4%)	
NSIP pattern	35 (28.9%)	16 (33.3%)	19 (26.0%)	
UCIP	12 (9.9%)	5 (10.4%)	7 (9.6%)	

Others***	4 (3.3%)	2 (4.2%)	2 (2.7%)	
Histological IPF guideline diagnosis				n/a
Definite UIP	28 (23.1%)	14 (29.2%)	14 (19.2%)	
Probable UIP	26 (21.5%)	5 (10.4%)	21 (28.8%)	
Indeterminate for UIP	38 (31.4%)	14 (29.2%)	24 (32.9%)	
Alternative diagnosis	29 (24.0%)	15 (31.3%)	14 (19.2%)	
Acute exacerbation before Bx	0 (0.0%)	0 (0.0%)	0 (0.0%)	n/a
Treatment				
Antifibrotic agents	40 (33.1%)	15 (31.3%)	25 (34.3%)	n/a
Immunosuppressants	42 (34.7%)	22 (45.8%)	20 (27.4%)	n/a

ANA, anti-nuclear antibody; ARS, aminoacyl-tRNA synthetase; Bx, biopsy; CHP, chronic hypersensitivity pneumonitis; CRP, C-reactive protein; CTD-ILD, connective tissue disease induced interstitial lung disease; DLCO, diffusing capacity of the lung for carbon monoxide; FVC, forced vital capacity; IPF, idiopathic pulmonary fibrosis; KL-6, Krebs von Lunge-6; LDH, lactate dehydrogenase; n/a, not applicable; NSIP, nonspecific interstitial pneumonia; UCIP, unclassifiable interstitial pneumonia; UIP, usual interstitial pneumonia; RF, rheumatoid factor.

* Score 3, predominant ciOP; Score 2, moderately developed ciOP; Score 1, minimal distribution of ciOP.

** Include smoking-related interstitial pneumonia and idiopathic pleuroparenchymal fibroelastosis

*** Include airway-centered interstitial fibrosis and pleuroparenchymal fibroelastosis

Table 2: Clinical outcomes

	All patients	With ciOP	Without ciOP	P value
Number	121	48	73	
AE after 12 months	1 (0.8%)	0 (0.0%)	1 (1.4%)	n/a
Change after 6 months				
Δ%FVC	+1.45 (-4.0-+8.5)	+4.5 (-0.5-+13.1)	+0.4 (-4.6-+5.9)	0.001
Δ%DLCO	+1.4 (-5.1-+7.9)	+5.9 (-4.0-+17.2)	+0.4 (-0.6-+7.2)	0.022
%ΔKL-6	-13.2 (-37.6-+4.8)	-25.9 (-48.2--2.0)	-10.2 (-31.0-+8.3)	0.043
ΔLDH	-5.0 (-29.0-+16.0)	-10.0 (-46.0-+16.0)	-2.0 (-27.0-+19.0)	n/a
Change after 12 months				
Δ%FVC	+1.2 (-5.1-+8.3)	+6.1 (-3.9-+11.0)	+0.4 (-7.1-+5.6)	0.035
Δ%DLCO	+0.5 (-6.3-+9.5)	+5.8 (-6.0-+17.1)	-1.6 (-8.0-+6.9)	0.040
%ΔKL-6	-13.9 (-42.2-+12.4)	-28.6 (-49.1--5.2)	-8.7 (-38.1-+17.2)	0.024
ΔLDH	-5.0 (-24.5-+17.5)	-10.0 (-41.0-+17.5)	-1.0 (-22.0-+18.0)	n/a

AE, acute exacerbation; DLCO: diffusing capacity of the lung for carbon monoxide; FVC, forced vital capacity; KL-6, Krebs von Lunge-6; LDH, lactate dehydrogenase

Table 3: Multivariate analysis

	All patients	With ciOP	Without ciOP	P value (univariate)	Odds ratio	P value (multivariate)
Number	121	48	73			
Baseline blood data						
KL-6 (IU/mL)	1211 (713-2007)	1495 (894-2360)	1055 (675-1716)	0.043	0.9997 (0.9994-1.0000)	n/a
Pulmonary function test (%)						
%FVC	88.1 (69.9-102.9)	96.5 (69.2-112.7)	85.1 (70.4-99.1)	n/a		
%DLCO	67.6 (55.1-81.0)	61.3 (51.3-73.8)	69.4 (59.7-83.5)	0.026	1.0239 (1.0019-1.0464)	n/a
BALF analysis cell fractionation (%)						
Macrophage	84.4 (66.1-92.0)	78.8 (46.8-90.0)	87.2 (69.1-93.8)	0.009	1.0234 (1.0054-1.0417)	n/a
Lymphocyte	8.0 (3.6-20.7)	10.8 (4.4-33.2)	6.4 (3.4-10.4)	0.005	0.9698 (0.9480-0.9920)	n/a
Change after 6 months						
Δ%FVC	+1.45 (-4.0-+8.5)	+4.5 (-0.5-+13.1)	+0.4 (-4.6-+5.9)	0.001	0.9338 (0.8933-0.9762)	0.001
Δ%DLCO	+1.4 (-5.1-+7.9)	+5.9 (-4.0-+17.2)	+0.4 (-0.6-+7.2)	0.016	0.9571 (0.9223-0.9933)	n/a
%ΔKL-6	-13.2 (-37.6-+4.8)	-25.9 (-48.2--2.0)	-10.2 (-31.0-+8.3)	n/a		

DLCO: diffusing capacity of the lung for carbon monoxide, FVC: forced vital capacity, KL-6: Krebs von Lunge-6

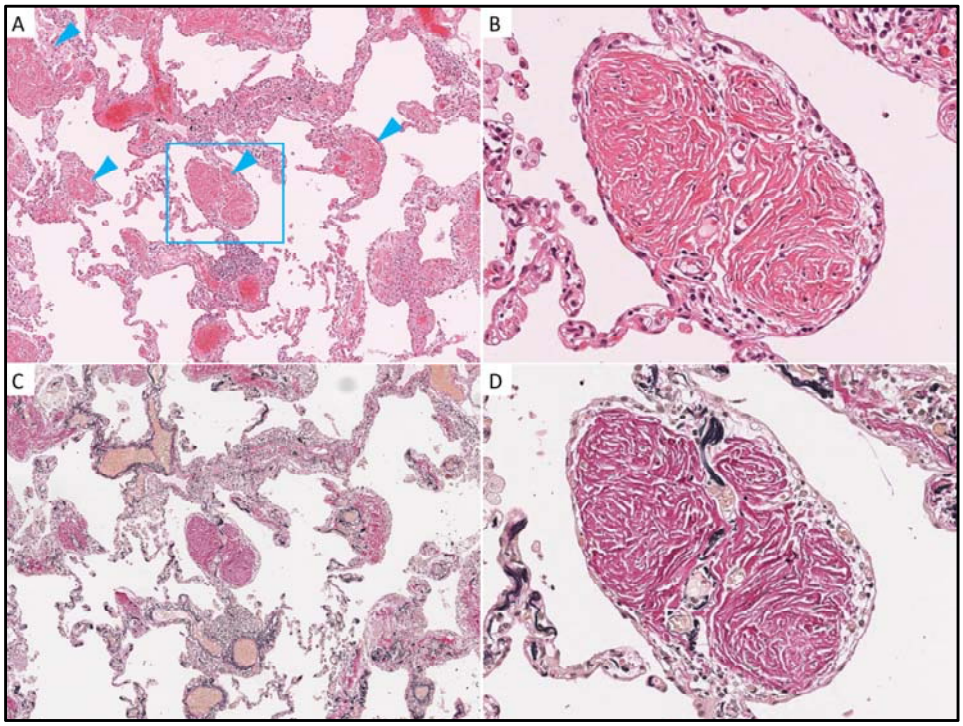


Figure 1

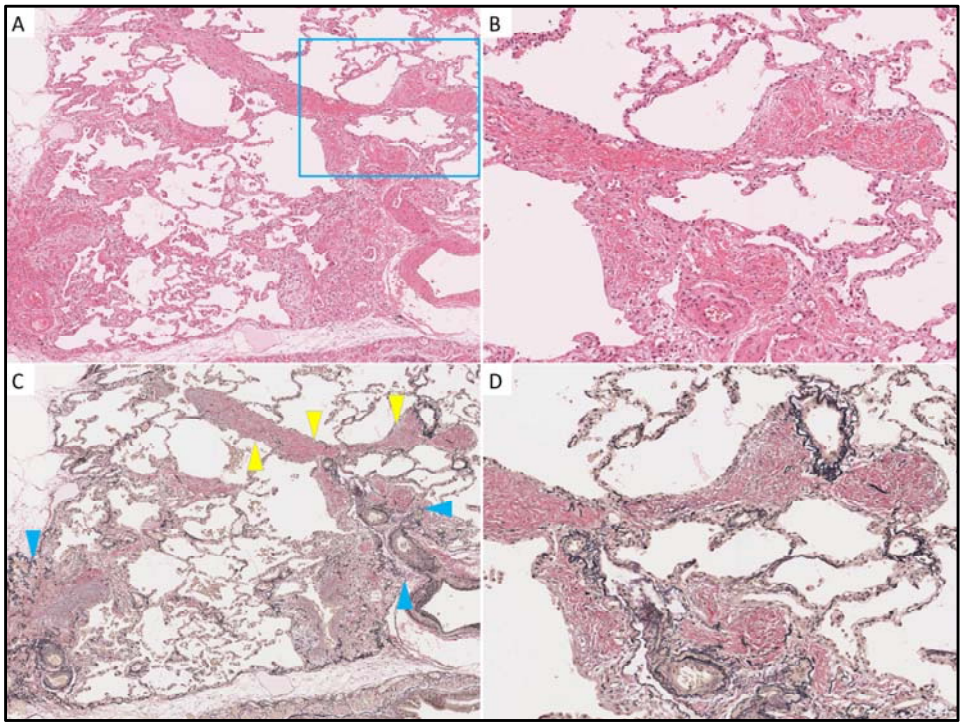


Figure 2

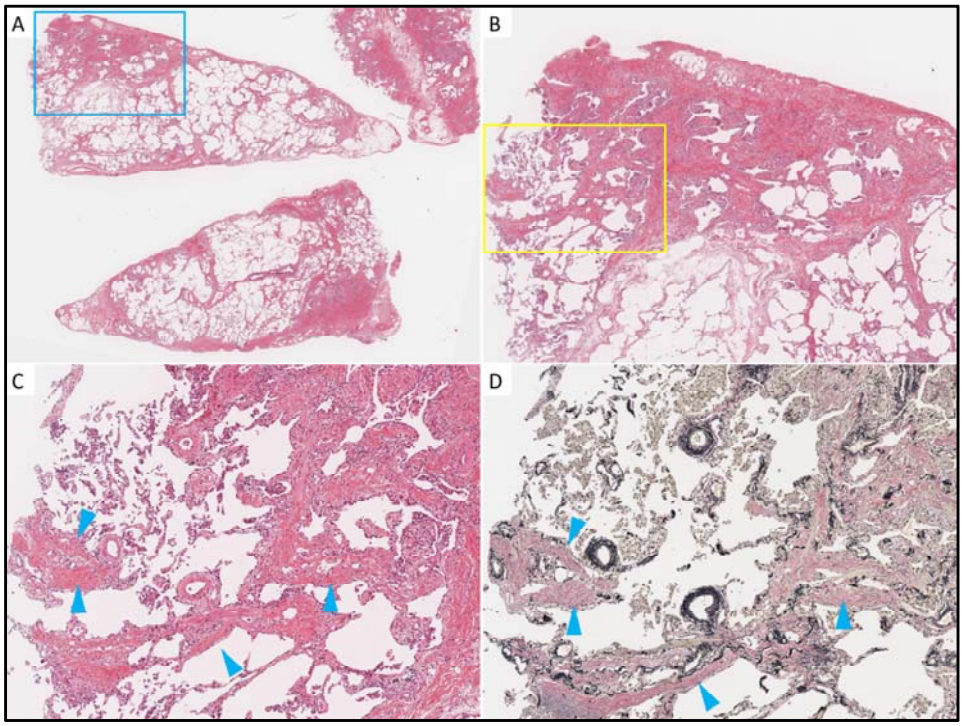


Figure 3

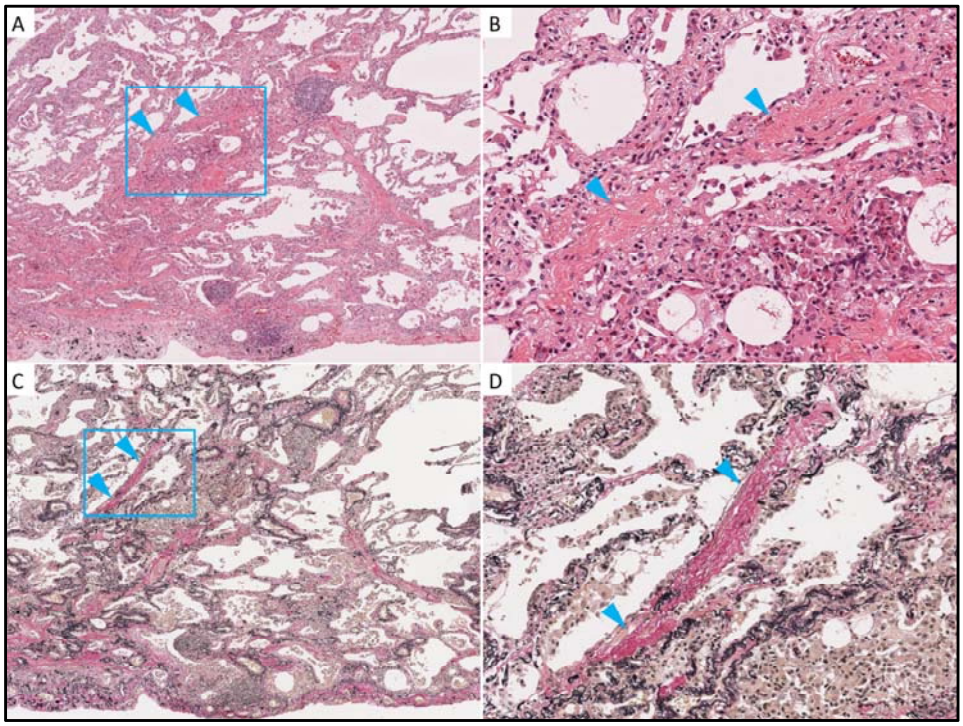


Figure 4

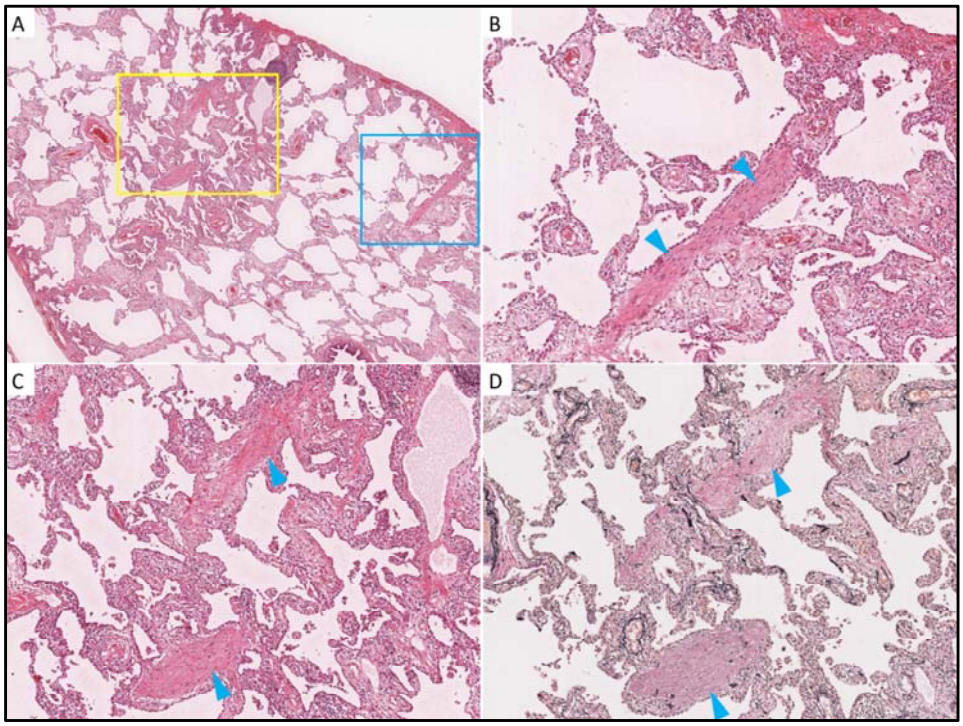


Figure 5

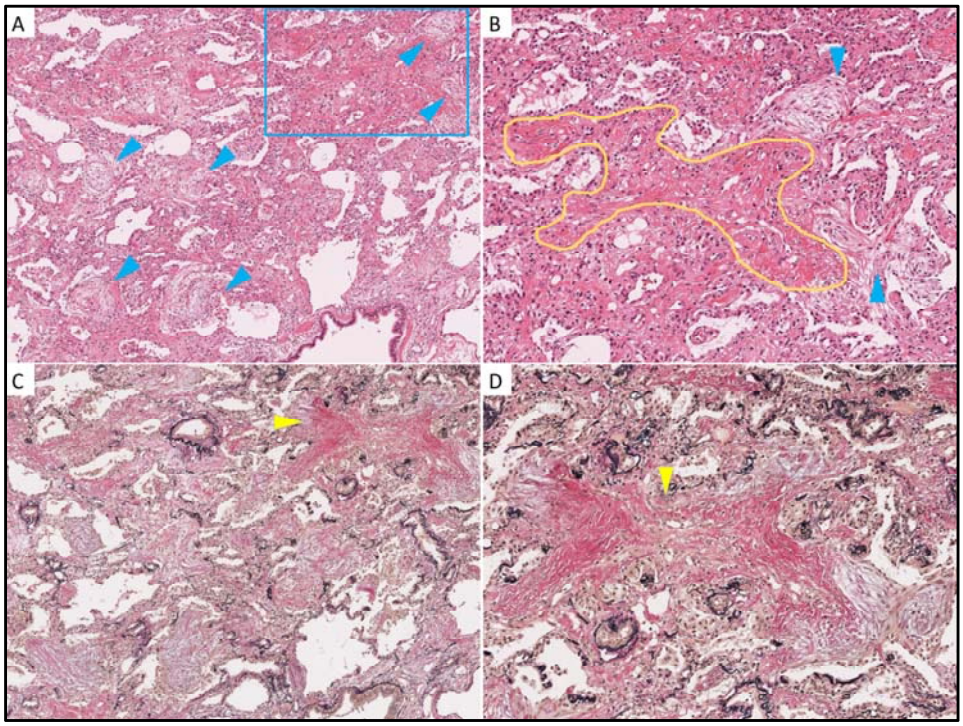
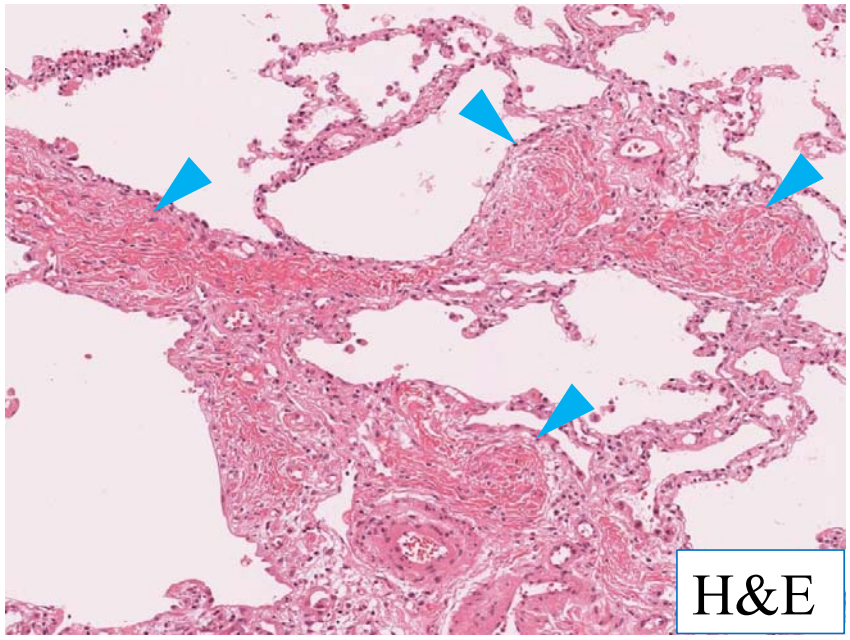
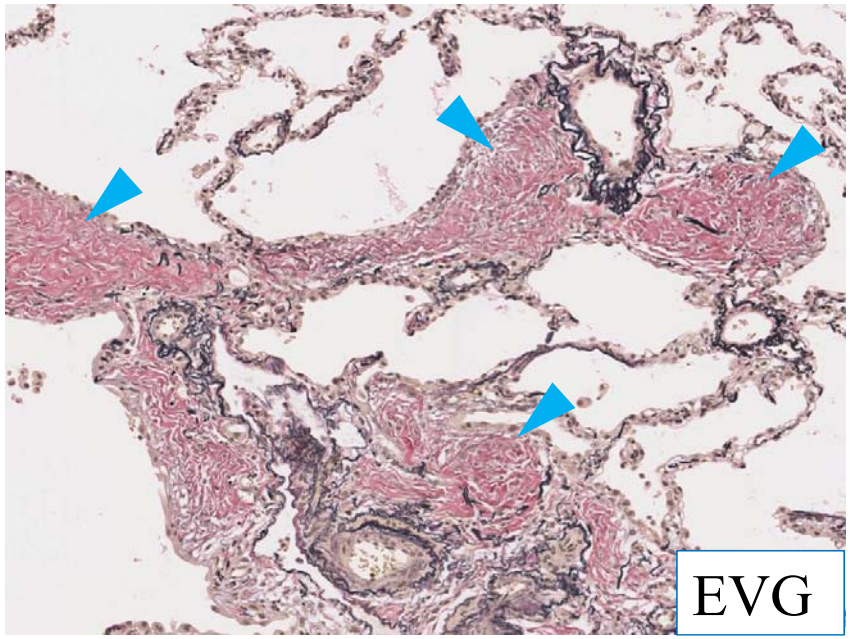


Figure 6

Cicatricial organizing pneumonia (ciOP)





ciOP is…
deposition of dense collagenous fibers within the alveolar space without destruction of the lung structure

ciOP is one of the histopathological findings seen in interstitial lung disease

ciOP was found in 39.7% (48/121) of fibrotic interstitial pneumonia

When ciOP mixed with fibrotic interstitial pneumonia, decline of forced vital capacity in pulmonary function test was small, and which suggest a good prognosis