

A retrospective clinical research of relapsed organizing pneumonia

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Abstract:

BACKGROUND: Organizing pneumonia (OP) usually responds spectacularly well to initial treatment, but relapses can occur and some cases run a fatal course. Still, the issue of relapse has been addressed in relatively few studies, and predictors have not been clarified. The purpose of this study was to examine the pattern of relapses in OP, to determine whether relapse affects morbidity and mortality, and to identify possible predictors of relapse.

METHODS: Blood sampling, pulmonary function testing, computed tomography (CT) of the chest, and bronchofiberscopy were performed for all patients and were retrospectively reviewed along with clinical information. Periodical chest CT was conducted and additional chest CT was performed when relapse of OP was clinically suspected. All patients were followed regarding treatment response, treatment duration, and presence of relapse. Results were compared between two groups based on serum concentrations of surfactant protein (SP)-D: normal SP-D and high SP-D.

RESULTS: Twenty-two patients were analyzed in this study. SP-D showed a negative correlation with percutaneous oxygen saturation and positive correlations with serum lactate dehydrogenase, Krebs von den Lungen (KL)-6, and percentage of lymphocytes in bronchoalveolar lavage (BAL). Prognosis was good for all patients, but relapse was significantly more frequent in the high SP-D group (6 cases) than in the normal SP-D group (0 cases; $P = 0.049$). Serum KL-6 and percentage of monocytes in BAL were significantly higher, and pulmonary vital capacity and forced expiratory volume in 1 s were significantly lower in the high SP-D group than in the low SP-D group.

CONCLUSIONS: When treating cases of OP with high serum concentrations of SP-D, attention should be paid to the possibility of relapse.

Keywords:

Monocytes, organizing pneumonia, relapse, surfactant protein-D

Organizing pneumonia (OP) is a type of diffuse interstitial lung disease (ILD) in which the pathological pattern was defined by the characteristic presence of buds of granulation tissue within the lumen of distal pulmonary airspaces, comprising fibroblasts and myofibroblasts intermixed with loose connective matrix. The process of intra-alveolar organization results from a sequence of alveolar injury, alveolar deposition of fibrin, and colonization of fibrin with proliferating fibroblasts.^[1]

OP can be classified into cryptogenic OP (COP), as the idiopathic form of OP mentioned in the American Thoracic Society (ATS) and European Respiratory Society (ERS) statements regarding the classification of idiopathic interstitial pneumonia (IP),^[2] and secondary OP (SOP), on the basis of underlying factors such as infection, pharmacotherapy, connective tissue disease, radiation, organ transplantation, and others.^[3] The clinical and radiographic findings, treatment response, and prognosis in patients with both COP and SOP are reported to be similar and nonspecific.^[4]

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OP usually responds spectacularly well to initial treatment and typically runs a benign course. However, relapses can occur and some cases do not completely resolve, with the potential for severe or fulminant respiratory failure requiring mechanical ventilation, occasionally leading to death. Onishi *et al.* reported that a high percentage of neutrophils in bronchoalveolar lavage (BAL) and the level of fibrin deposition in lung biopsy specimens were considered as predictors of OP relapse during tapering or after cessation of steroid therapy.^[5] Lazor *et al.* retrospectively studied 48 cases of COP and reported that delayed treatment increased the risk of relapse.^[6] The issue of relapse has been addressed in relatively few studies, and predictors have yet to be clarified.

Among the blood biomarkers, Krebs von den Lungen (KL)-6 and surfactant protein (SP)-D have been widely used in clinical practice.^[7] KL-6 is a high-molecular-weight, circulating glycoprotein recently classified in humans as MUC1 mucin.^[8] In a previous study, KL-6 was suggested as a useful marker in differentiating between ILD, evaluation of disease activity, and prediction of disease outcome.^[9] SP-D belongs to the collectin subgroup of the C-type lectin superfamily^[10] and is also reportedly useful as a biomarker of ILD.^[11] Although both biomarkers are derived from regenerating alveolar epithelial type II cells (AECIIs), discrepancies between them have been reported.^[12] The discrepancies between serum KL-6 and SP-D may be due to the different sources of KL-6 and SP-D. SP-D is expressed in mature AECIIs, whereas KL-6 is expressed in the initial phase, before SP-D is expressed.^[13]

In OP, Yamaguchi *et al.* reported that chest X-ray scores correlated with serum KL-6 levels, and patients needing treatment with prednisolone were included in the high KL-6 group.^[14] Hara *et al.* suggested that OP with elevated serum KL-6 may be more severe and unstable than that with normal serum KL-6,^[15] and Okada *et al.* reported the frequency of relapse as higher in patients with an elevated KL-6 level than in those with a normal KL-6 level.^[16]

SP-D is a good predictor of prognosis in patients with idiopathic pulmonary fibrosis (IPF),^[17-19] but few reports have clarified associations with SP-D or OP. The objectives of this study were to examine patterns of relapse in OP, to determine whether relapses affect morbidity and mortality rates, and to identify possible predictors of relapse.

Methods

Subjects

It is an observational, retrospective study. This study received ethical approval from the special

committee of Toho University Ohashi Medical Center (project registration number H17081) to proceed between 2011 and 2017. Prior to enrollment, each patient provided written informed consent to participate. Eligible participants were adults with OP pathologically confirmed from transbronchial lung biopsy under bronchofiberscopy (BF) or surgical lung biopsy. OP was classified into COP and SOP on the basis of the identification of underlying diseases.

Study design

Blood sampling (white blood cell count, lactate dehydrogenase [LDH], C-reactive protein, KL-6, and SP-D), pulmonary function testing (vital capacity [VC], percentage of predicted VC [%VC], forced expiratory volume in 1 s [FEV₁], and FEV_{1.0}/forced VC ratio), carbon monoxide diffusing capacity, computed tomography (CT) of the chest, and BF were performed for all patients and were retrospectively reviewed along with clinical information. Periodical chest CT was conducted and additional chest CT was performed when relapse of OP was clinically suspected. Two experienced respiratory physicians and two radiologists evaluated cases to diagnose relapsed OP. Relapsed OP was defined as the presence of abnormal shadows in the absence of other causes based on clinical examinations. As OP is consisted with nonspecific radiographic findings and there is no established imagine classification, imaging findings were classified using high-resolution CT criteria for usual interstitial pneumonia (UIP) pattern according to the guidelines of ATS/ERS/JRS/ALAT (subpleural basal predominance, reticular abnormality, honeycombing, upper or mid-lung predominance, peribronchovascular predominance, extensive ground-glass abnormality, profuse micronodules, discrete cysts, diffuse mosaic attenuation/air-trapping, and consolidation in bronchopulmonary segments). BF (BF-1T30; Olympus, Tokyo, Japan) was performed under standard premedication and local anesthesia. BAL was performed at a selected site at the presence of abnormal shadow. Total cell counts, cellular components, and concentrations of the ratio of CD4/CD8 T-lymphocytes in BAL fluid were determined. Simultaneously, blood tests including serum KL-6 and SP-D levels were determined, and pulmonary function testing (FUDAC-77®; Fukuda Denshi; Tokyo, Japan) was performed. Total cell count was determined using a Bürker chamber, and the differential cell count was evaluated under light microscopy on May-Grunwald-Giemsa-stained slides. The ratio of CD4/CD8 T-lymphocytes was determined using flow cytometric analysis with monoclonal anti-CD4 and anti-CD8 antibodies (Becton Dickinson and Co., Franklin Lakes, New Jersey, USA). SP-D and KL-6 were measured by Enzyme immuno assay (EIA) (Eidea, Tokyo, Japan). Detection limits were 17.3 pg/mL and

0 ng/ml, respectively. Results were compared between groups based on serum SP-D levels (normal, 0–109.9 ng/mL) into normal SP-D and high SP-D groups.

All patients were followed regarding treatment response, treatment duration, and presence of relapse.

Analysis

Results are expressed as mean ± standard deviation. Correlations between SP-D and each parameter were examined by Spearman’s rank-order correlation. To clarify differences between the normal and high SP-D groups, discrete variables were examined using Pearson’s Chi-square test and continuous variables were examined using the Wilcoxon rank-sum test. All statistical analyses were performed using SPSS Statistics (Japan IBM; Tokyo, Japan). Values of $P < 0.05$ were considered statistically significant.

Results

Twenty-two patients were analyzed in this study. The mean age was 71 ± 8 years, and the underlying pathology was COP in 10 patients and SOP in 12 patients. Causes of SOP were rheumatoid arthritis in four patients, adverse effects of pharmacotherapy in two patients, radiation exposure in two patients, and severe pneumonia in two patients. SP-D showed a negative correlation with percutaneous oxygen saturation and positive correlations with serum LDH, KL-6, and percentage of lymphocytes in BAL [Figures 1 and 2]. Comparisons between COP and SOP showed no significant differences in any variables (data not shown).

The SP-D group comprised 7 patients and the high SP-D group comprised 15 patients. No significant differences were seen between the groups in terms of

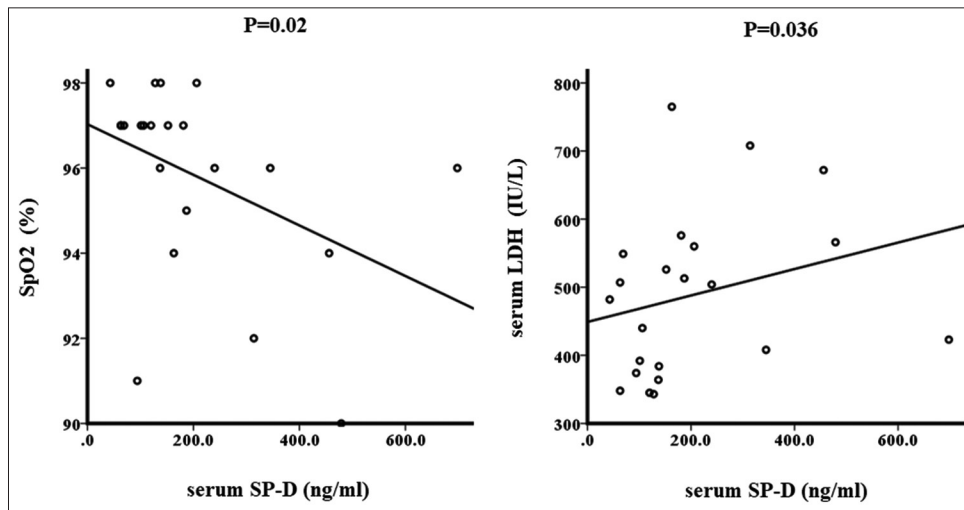


Figure 1: Correlations of SpO2 and LDH with the levels of serum SP-D. Serum SP-D showed a negative correlation with SpO2 and showed a positive correlation with serum LDH. LDH=Lactate dehydrogenase, SP-D=Surfactant protein-D, SpO2=Percutaneous oxygen saturation

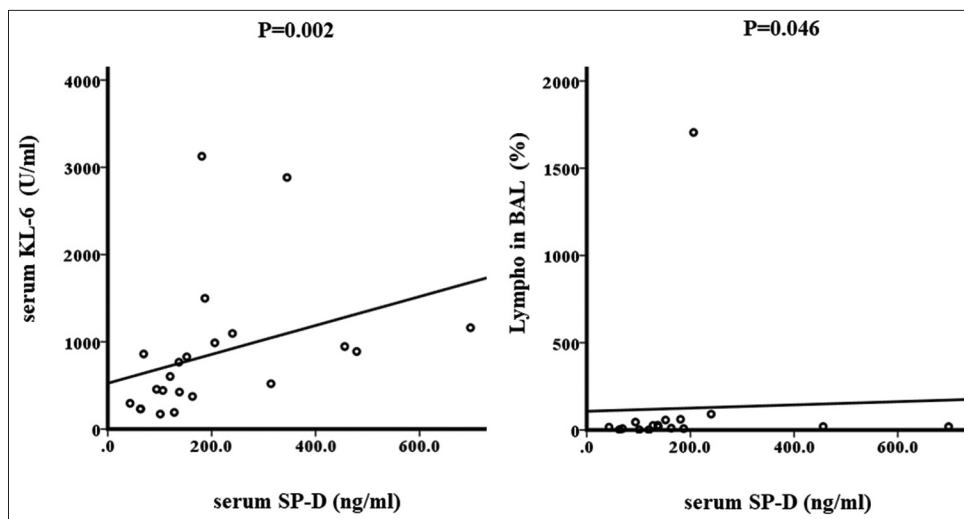


Figure 2: Correlations of serum KL-6 and lymphocytes in BAL with the levels of serum SP-D. Serum SP-D showed a positive correlation with serum KL-6 and lymphocytes in BAL. BAL=Bronchoalveolar lavage, KL-6=Krebs von den Lungen-6, lympho=Lymphocytes, SP-D=Surfactant protein-D

patient background and necessity for and duration of treatment. The prognosis was good for all patients, but relapse was significantly more frequent in the high SP-D group (6 cases) than in the normal SP-D group (0 cases; $P = 0.049$) [Table 1].

The high SP-D group showed significantly higher serum concentrations of KL-6 and percentage of monocytes in BAL and significantly decreased pulmonary VC and FEV_{1.0} [Figures 3 and 4]. No significant differences were seen in imaging findings (data not shown). In addition, no significant differences between the normal and high KL-6 groups were seen in any variables (data not shown).

Table 1: Patients' characteristics, treatment regimens and outcomes*

Variable	Normal serum SP-D	Elevated serum SP-D	P
Patients (n)	7	15	
Age (years)	69.4±8.9	72.6±7.6	0.532
Sex male/female	4/3	11/4	0.447
Etiology			
Cryptogenic	4	6	0.452
Secondary	3	9	0.452
Rheumatoid arthritis	2	3	0.655
Drug	0	3	0.209
Radiation therapy	0	2	0.311
Severe pneumonia	1	1	0.563
Treatment			
Prednisolone	5	12	0.655
No treatment	2	3	0.655
Outcomes			
Improved	7	15	1.000
Deteriorated	0	0	1.000
Death	0	0	1.000
Recurrence	0	6	0.049

*Data are represented as mean±SD. SD=Standard deviation, SP-D=Surfactant protein-D

Discussion

In our study, the high SP-D group showed a significantly higher relapse rate and significantly decreased pulmonary VC and FEV_{1.0}. Although VC is already known to be decreased in ILD^[20] and a rapid decrease in %VC has been reported as a risk factor for acute exacerbation of IPF,^[21] relatively few studies have investigated the relationship between ILD and FEV_{1.0}. Milne *et al.* reported that the frailty index was associated with FEV_{1.0} in a patient with fibrotic ILD.^[22] Parra *et al.* used histochemistry, immunohistochemistry, and morphometric analysis to evaluate collagen/elastic fibers and immune cells in the bronchiolar interstitium on open lung biopsies in patients with COP. Multivariate analysis showed a decreasing risk of death from COP with high FEV_{1.0}.^[23] We, therefore, considered that the relationship between collagen/elastic fibers, immune cells, and FEV_{1.0} might have contributed to the relapse of OP.

Although Onishi *et al.* reported a high percentage of neutrophils in BAL as a predictor of OP relapse,^[5] our study found that the percentage of monocytes in BAL was significantly higher in the high SP-D group, which showed a significantly higher relapse rate. Several reports have suggested that the development of fibrosis is associated with activation of monocytes.^[24-26] Monocytes comprise a variety of subsets with diverse functions. Satoh *et al.* showed that Ceacam1+Msr1+Ly6C⁻F4/80-Mac1+ monocytes, which they termed "segregated-nucleus-containing atypical monocytes" (SatM), are regulated by CCAAT/enhancer-binding protein-β (Cebpb) and are critical for fibrosis. Cebpb deficiency results in a complete lack of SatM, and the development of bleomycin-induced fibrosis (but not inflammation) was prevented in chimeric mice with Cebpb^{-/-} hematopoietic cells.

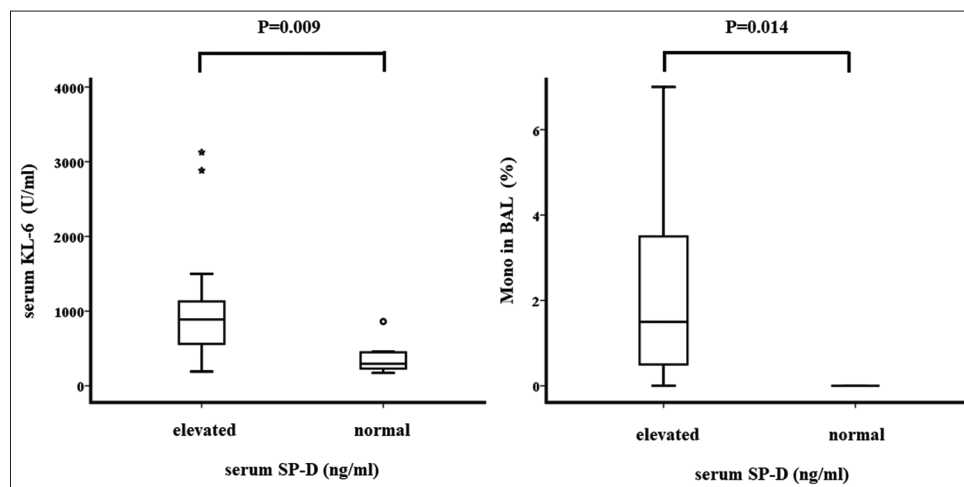


Figure 3: Comparison between the levels of serum SP-D in serum KL-6 and monocytes in BAL. In high SP-D group, serum KL-6 and monocytes in BAL were significantly higher. BAL=Bronchoalveolar lavage, mono=Monocytes, KL-6=Krebs von den Lungen-6, SP-D=Surfactant protein-D

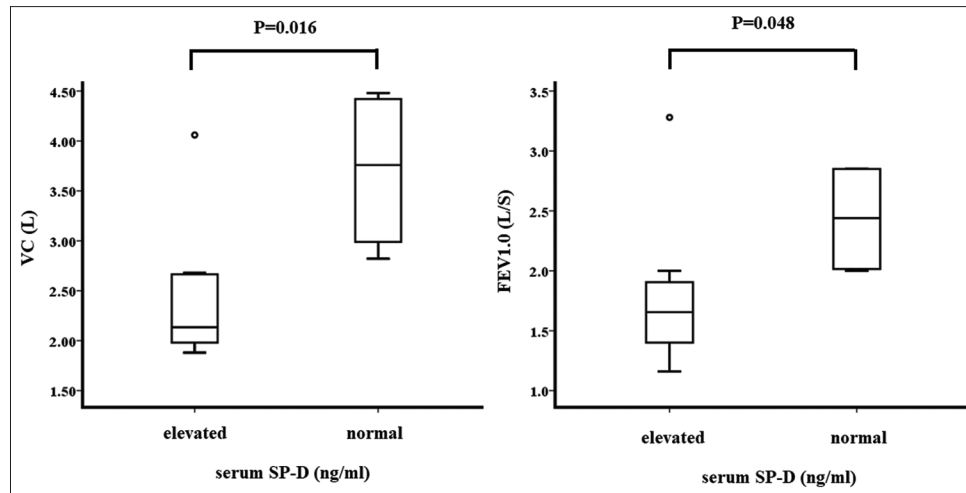


Figure 4: Comparison between the levels of serum SP-D in pulmonary function test. High SP-D group showed significant decreases in pulmonary VC and FEV_{1.0}. FEV_{1.0}=Forced expiratory volume in 1 s, SP-D=Surfactant protein-D, VC=Vital capacity

Adoptive transfer of SatM into *Cebpb*^{-/-} mice resulted in fibrosis and showed that SatM is critical for fibrosis.^[24] Several reports have noted that fibrocytes, which are spindle-shaped fibroblast-like cells that differentiate from a subpopulation of CD14⁺ monocytes, are associated with induction of fibrosis. Phillips *et al.* showed that CD45⁺Col I⁺CXCR4⁺ fibrocytes contribute to the pathogenesis of pulmonary fibrosis. In the murine model of bleomycin-induced pulmonary fibrosis, marked collagen deposition was observed after bleomycin exposure and represented the peak period of CD45⁺Col I⁺CXCR4⁺ fibrocyte infiltration.^[25] Moeller *et al.* reported that a threefold increase in circulating fibrocytes (CD45⁺Col-11 cells) was observed in patients with stable IPF compared with healthy control individuals. During episodes of acute disease exacerbation, fibrocyte counts further increased to an average of 15% of peripheral blood leukocytes and returned to preexacerbation levels in patients who recovered.^[26]

Although the relationship between SP-D and monocytes remains unclear, Jiang *et al.* reported that depletion of circulating monocytes by intravenous injection of CL 2 days before intratracheal lipopolysaccharide (LPS) treatment significantly reduced SP-D in the lungs of mice treated with intratracheal LPS for 2 days^[27] and Hirano *et al.* reported that SP-D deficiency reduced blood monocytes in atherosclerosis-prone apolipoprotein E-knockout mice.^[28] We, therefore, considered that elevation of SP-D was involved in the elevation of monocytes and that the development of fibrosis associated with monocyte activation played a role in the relapse of OP.

The study had several limitations. As the data came from a relatively small number of patients with a variety

of underlying diseases, the results could have been influenced by confounders such as types of concurrent medication. The statistical power of this study was 0.5. As OP is relatively rare disease, sample sizes were small in previous studies despite the participants collected for more than 10 years or in several hospitals.^[6,29,30] The number of registered patients in this study was small because this was conducted in one hospital in short period. Despite this limitation, we believe that this study has valuable implications for clinical practice. Another limitation was the lack of surgical lung biopsy. To obtain sufficient tissue for the pathologist to exclude other processes, such as nonspecific interstitial pneumonia or UIP, lung biopsy should be preferably performed through video-assisted thoracoscopic surgery or open thoracotomy rather than transbronchial biopsy.^[31] On the other hand, some reports have suggested that diagnosis can be made on the basis of transbronchial biopsy in a patient with typical clinical and radiologic features.^[32,33]

Conclusions

Patients with elevated serum levels of SP-D in OP showed significant increases in serum KL-6 and monocytes in BAL and showed significant decreases in pulmonary VC and FEV_{1.0}. The high SP-D group showed a significantly higher relapse rate than the normal SP-D group. These findings suggest that attention should be paid to the risk of relapse when treating OP in patients with a high serum concentration of SP-D.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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