【 ORIGINAL ARTICLE 】

Ground Glass Opacity with Mixed Consolidation on Chest Computed Tomography Reflects the Severe Condition of Pneumocystis Pneumonia in Association with a Poor Prognosis in Patients with Connective Tissue Diseases

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Abstract:

Objective   Pneumocystis pneumonia (PCP) is a serious fungal infection that can be life threatening in immunocompromised hosts. We evaluated the association between the radiological patterns of PCP on high-resolution computed tomography (HRCT) and clinical characteristics and the prognosis of patients with connective tissue disease (CTD).

Methods   All CTD patients who developed PCP from January 1999 to April 2017 were retrospectively evaluated. Patients were divided into three groups based on their chest HRCT findings: Ground glass opacity (GGO) sharply demarcated from the adjacent normal lung by interlobular septa (demarcated GGO), diffuse GGO without obvious demarcation (diffuse GGO), and GGO with mixed consolidation (mixed GGO). We compared the clinical characteristics at the onset of PCP and the outcomes among the groups.

Results   A total of 35 cases were identified: demarcated GGO (n=8, 23%), diffuse GGO (n=19, 54%), and mixed GGO (n=8, 23%). The mixed GGO group showed a higher serum C-reactive protein level (p<0.0001), lower lymphocyte count (p=0.07), lower serum albumin (p<0.001), and lower partial pressure of arterial oxygen/fraction of inspiratory oxygen ratios (p<0.001) in comparison to the demarcated and diffuse GGO groups. The mixed GGO group showed significantly higher mortality in comparison to the demarcated and diffuse GGO groups (88% vs. 7%, p<0.0001).

Conclusion   GGO with mixed consolidation on chest HRCT was associated with a poor outcome of PCP in patients with CTD.

Key words: pneumocystis pneumonia, mortality, connective tissue disease, high-resolution computed tomography, consolidation

Introduction

Pneumocystis pneumonia (PCP) is a serious infection that causes immense inflammation of the lungs with potentially fatal consequences in immunocompromised hosts such as patients with human-immunodeficiency virus (HIV) infection or patients receiving immunosuppressive treatment (1, 2). PCP is also a common opportunistic condition in patients with connective tissue diseases (CTDs), and the resultant respiratory failure is more severe in such patients than in those infected with HIV (3). High-resolution computed tomography (HRCT) of the lungs is an essential tool that reveals various findings in the diagnosis and assessment of PCP. However, the condition can be classified into three patterns based on the distribution of ground-glass opacity (GGO) (4) as GGO sharply demarcated from the adjacent normal lung by interlobular septa, diffuse GGO without obvious demarcation, and GGO with mixed consolidation. The distinct patterns have been suggested to reflect different pathogenic reactions to *Pneumocystis jiroveci*. Nonetheless, little is known about the frequency or the clinical features of

Figure. **Representative findings of three patterns of PCP detected on high resolution computed tomography. (a) GGO sharply demarcated from the adjacent normal lung by interlobular septa (Demarcated GGO), (b) Diffuse GGO without obvious demarcation (Diffuse GGO), (c) GGO with mixed consolidation (Mixed GGO). PCP: pneumocystis pneumonia, GGO: ground glass opacity**

PCP according to each radiological type in patients with CTD. In the present study, we evaluated the association between the radiological patterns of PCP on chest HRCT; and the clinical characteristics and prognosis of patients with CTD.

Materials and Methods

We retrospectively reviewed all consecutive patients who developed PCP during immunosuppressive treatment for underlying CTDs at our institution from January 1999 to April 2017. Definite PCP was defined based on the criteria outlined in a previous report (5), based on the fulfillment of the following criteria: (i) clinical respiratory manifestations, (ii) GGO on chest HRCT, (iii) microscopic detection of *Pneumocystis jiroveci* or positive polymerase-chain-reaction test results for *Pneumocystis jiroveci* deoxyribonucleic acid in respiratory specimens, (iv) increased serum β-D glucan levels (turbidimetric kinetic method, Wako Pure Chemical Industries, Tokyo, Japan), and (v) exclusion of other types of infectious pneumonitis caused by bacteria, viruses, or fungi. The presence of other types of infectious pneumonitis was determined by each attending physician based on sputum and blood cultures, urinary/blood antigens, and/or antibody measurement.

The demographic characteristics and laboratory findings at the onset of PCP were collected from patient charts. Chest HRCT findings were evaluated by two investigators (MA and YK) based on the radiologist's radiograph interpretation report. Chest HRCT findings were classified into three patterns described in a previous study (4): GGO sharply demarcated from the adjacent normal lung by interlobular septa (demarcated GGO), diffuse GGO without obvious demarcation (diffuse GGO), and demarcated or diffuse GGO with mixed consolidation (mixed GGO) (Figure). There was consensus among the two investigators regarding the classification of the patterns. The clinical characteristics and prognosis of the included patients were investigated.

The Ethics Committee of Keio University School of Medicine approved this study. The requirement for written informed consent was waived based on Japanese guidelines. All investigations were conducted according to the princi-

ples of the Declaration of Helsinki.

Statistical analyses

Continuous variables were compared using Student's t-test. Categorical variables were analyzed by the chi-squared test. P values (two-sided) of <0.05 were considered to indicate statistical significance. All statistical analyses were performed using the EZR software program (Saitama Medical Center, Jichi Medical University, Saitama, Japan) (6).

Results

A total of 35 patients with PCP were identified and divided into three groups based on the HRCT findings as follows: demarcated GGO (n=8, 23%), diffuse GGO (n=19, 54%), and mixed GGO (n=8, 23%). The patient demographics at the onset of PCP are presented in Table. No patient was under prophylaxis with trimethoprim-sulfamethoxazole against PCP. The underlying connective tissue diseases included rheumatoid arthritis (n=19, 54%), systemic lupus erythematosus (n=9, 26%), vasculitis (n=6, 17%), and mixed connective tissue disease (n=1, 3%). The prevalence of underlying connective tissue diseases and their treatments, including glucocorticoids, biologic agents, methotrexate, and other immunosuppressants did not differ among the demarcated GGO, diffuse GGO, and mixed GGO groups. Furthermore, there were no significant differences among the three groups in the incidence of comorbidities such as renal dysfunction, lung disease, cardiac disease, and liver dysfunction.

When patients of the non-mixed GGO (demarcated and diffuse GGO) groups were compared with those of the mixed GGO group, we found a significant difference in the clinical and laboratory findings. The presentation of PCP was more acute in patients with a mixed GGO pattern than in those without (duration from the onset to the diagnosis: 5 days vs. 13 days, p=0.06). Laboratory tests showed that the mixed GGO group had a higher serum C-reactive protein level (17.1 mg/dL vs. 4.5 mg/dL, p<0.0001), lower lymphocyte count (379/μL vs. 802/μL, p=0.07), lower serum albumin level (2.1 g/dL vs. 3.0 g/dL, p<0.001), and lower partial pressure of arterial oxygen (PaO_2)/fraction of inspiratory

Table. Comparison of the PCP Patients Stratified by the Radiological Findings.

Characteristics	Non-mixed GGO n=27			Mixed GGO n=8	p value (Mixed GGO vs. non-mixed GGO)
	Demarcated GGO n=8	Diffuse GGO n=19	Total non-mixed GGO n=27		
Age, years, mean (SD)	60 (15)	65 (14)	63 (14)	65 (18)	ns
Female, n (%)	8 (100)	10 (53)	18 (67)	6 (75)	ns
Duration from onset of symptoms to diagnosis, days, mean (SD)	12 (10)	13 (11)	13 (11)	5 (3)	0.06
Smoking, n (%)	1 (13)	7 (37)	8 (30)	1 (13)	ns
Underlying disease, n (%)					ns
Rheumatoid arthritis	4 (50)	12 (63)	16 (59)	3 (38)	
Systemic lupus erythematosus	3 (38)	4 (21)	7 (26)	2 (25)	
Vasculitis	0 (0)	3 (16)	3 (11)	3 (38)	
Mixed connective tissue disease	1 (13)	0 (0)	1 (4)	0 (0)	
Comorbidity, n (%)					
Renal dysfunction‡	4 (50)	11 (58)	15 (56)	4 (50)	ns
Lung disease‡‡	2 (25)	7 (37)	9 (33)	4 (50)	ns
Cardiac disease‡‡‡	2 (25)	0 (0)	2 (7)	2 (25)	ns
Liver dysfunction‡‡‡‡	5 (50)	3 (16)	8 (30)	5 (63)	ns
Treatment for CTD					
Glucocorticoids, n (%)	5 (63)	16 (84)	21 (78)	8 (100)	ns
Dose of prednisolone (mg/day), mean (SD)	17 (22)	13 (14)	14 (16)	20 (9)	ns
Biologic agents, n (%)	1 (13)	7 (37)	8 (30)	1 (13)	ns
Methotrexate, n (%)	4 (50)	10 (53)	14 (52)	3 (38)	ns
Other immunosuppressants, n (%)	4 (50)	8 (42)	12 (42)	3 (38)	ns
Laboratory findings					
PaO$_2$/FiO$_2$ ratio, mean (SD)	281 (94)	348 (88)	328 (93)	177 (87)	<0.001
Lymphocytes (/μL), mean (SD)	773 (835)	814 (484)	802 (592)	379 (459)	0.07
Albumin, g/dL, mean (SD)	2.9 (0.4)	3.0 (0.6)	3.0 (0.6)	2.1 (0.3)	<0.001
LDH, U/L, mean (SD)	585 (399)	366 (193)	431 (281)	483 (110)	ns
CRP, mg/dL, mean (SD)	3.6 (2.5)	4.9 (4.7)	4.5 (4.1)	17.1 (10.7)	<0.0001
IgG, mg/dL, mean (SD)	1,122 (242)	939 (432)	994 (389)	914 (616)	ns
KL-6, U/mL, mean (SD)	1,240 (884)	991 (695)	1,067 (746)	1,039 (697)	ns
β-D glucan, pg/mL, mean (SD)	149 (137)	215 (191)	195 (177)	201 (166)	ns
Treatment regimen for PCP					
Pulse or high dose therapy of glucocorticoids, n (%)	6 (75)	13 (68)	19 (70)	8 (100)	ns
High dose of TMP-SMZ (15-20 mg/kg/day of TMP), n (%)	4 (50)	8 (42)	12 (44)	5 (63)	ns
Death, n (%)	2 (25)	0 (0)	2 (7)	7 (88)	<0.0001

‡eGFR<60 mL/min/1.73 m^2. ‡‡Lung disease: interstitial lung disease, bronchiolitis, and chronic obstructive pulmonary disease. ‡‡‡Cardiac disease: the past history of heart failure, ischemic heart disease, and heart amyloidosis. ‡‡‡‡Liver dysfunction: alanine aminotransferase is over 37 IU/L. PCP: pneumocystis pneumonia, CTD: connective tissue disease, GGO: ground glass opacity, SD: standard deviation, ns: non-significant, KL-6: Krebs von den Lungen-6, LDH: lactate dehydrogenase, CRP: C-reactive protein, TMP-SMZ: trimethoprim-sulfamethoxazole

oxygen (FiO$_2$) ratio (177 vs. 328, p<0.001) in comparison to the other groups.

No significant differences were observed in the other demographic characteristics of the non-mixed and mixed GGO groups, including age (65 years vs. 63 years, p=0.83), Krebs von den Lungen-6 level (1,039 U/mL vs. 1,067 U/mL, p=0.95), lactate dehydrogenase level (483 U/L vs. 431 U/L, p=0.62), and β-D glucan level (201 pg/mL vs. 195 pg/mL, p=0.94).

Among the eight patients with mixed GGO, seven patients satisfied the Berlin definition criteria for acute respiratory distress syndrome (ARDS) (7). Consolidation was distributed predominantly in a dorsal location in seven of the eight cases of mixed GGO. Of note, patients with mixed GGO pattern showed a significantly higher mortality rate in comparison to those with a non-mixed GGO pattern (88% vs. 7%, p<0.0001). The treatment regimens for PCP (e.g., steroid pulse or high-dose glucocorticoids and high-dose trimethoprim-sulfamethoxazole) did not differ between the mixed and non-mixed GGO groups.

The mortality rate was 21% in rheumatoid arthritis (4/19), 50% in vasculitis (3/6), and 22% in systemic lupus erythematosus (2/9). Of the nine deaths, three (33%) were in patients with preexisting respiratory involvement (one rheumatoid arthritis patient with interstitial lung disease, one vasculitis patient with interstitial lung disease, and one vasculitis patient with chronic obstructive pulmonary disease).

Discussion

In the present study, we found that the presence of GGO with consolidation was associated with a higher serum C-reactive protein level, a lower serum albumin level and a lower PaO$_2$/FiO$_2$ ratio in comparison to GGO without consolidation. We also found that patients showing GGO with consolidation were more likely to have fatal outcomes in comparison to those without consolidation. Our results suggest that the radiological finding of GGO with consolidation on HRCT reflects a more severe condition and a poor prognosis of PCP in patients with CTDs.

Our study showed that diffuse GGO was the main HRCT finding (54%) of PCP in CTD patients, which is in line with a previous report (8). Kanne et al. reported that diffuse GGO was the principal finding of PCP and reflected intra-alveolar fibrin, debris, and the accumulation of the organism (8). We also demonstrated that PCP in CTD patients can present with consolidation on HRCT and that this was associated with a poor prognosis. These findings validated the recent studies that reported consolidation and crazy-paving pattern as poor prognostic radiological findings in non-HIV patients (9, 10). It would have been interesting to investigate the effect of the extent of consolidation area on the prognosis of PCP in CTD patients; however, the sample size of our study was too small for such an investigation. Future studies that semi-quantitatively evaluate consolidation will promote the more detailed stratification of the prognosis.

Several hypotheses could explain the mechanism of association between mixed GGO and increased severity such as rapid progression, a higher level of serum C-reactive protein level, and a lower PaO$_2$/FiO$_2$ ratio, along with a higher mortality rate. First, a stronger neutrophilic inflammatory response against *Pneumocystis jiroveci* might be unleashed in patients with mixed GGO than in those without. A study on clinicopathological comparisons between HIV and non-HIV PCP patients reported that non-HIV patients had more intensive neutrophilic inflammation in their bronchoalveolar lavage fluid, despite having lower amounts of *Pneumocystis jiroveci*; however, the underlying pathogenesis remains unclear (11). The study also showed that in non-HIV patients with PCP, the clinical course was more acute and severe, and that the prognosis was worse (11). Importantly, another study demonstrated that consolidation on HRCT was observed in half of non-HIV PCP patients but no HIV patients with PCP (12). These studies suggest the possibility that consolidation on HRCT is associated with more neutrophilic inflammation in the lungs and a poor prognosis. Thus, we assumed that more intense neutrophilic inflammation against *Pneumocystis jiroveci* in the lungs occurred in the mixed GGO group in comparison to the non-mixed GGO group in the present study. A second hypothesis is that consolidation occurs due to ARDS. Patients in the present study with consolidation had lower serum albumin levels, which is consistent with the previous studies that consider low levels to be

a prognostic factor for PCP (13) and a factor predicting the severity of ARDS (14). Assuming that hypoalbuminemia, severe respiratory failure, and dense opacification on HRCT are likely to represent severe edema and protein exudation within the interstitium and alveoli without cardiac failure, the poor prognosis observed in cases of mixed GGO might be ascribed to a severe condition similar to ARDS. In fact, the majority of cases in the mixed GGO group satisfied the Berlin definition criteria for ARDS. In accordance with the treatment of ARDS-although not yet established-patients with PCP with consolidation on HRCT should immediately receive intensive treatment with proper breathing support, nutritional supply, and measures to prevent secondary infection in addition to receiving treatment for PCP. The possibility of co-infection with other pathogens also remained; however, we excluded patients in whom infections other than PCP had been clinically recognized. Since the pathogenesis and mechanisms underlying the association between consolidation and a poor prognosis remain unclear, the accumulation of cases and relevant studies is needed.

The present study was associated with some limitations, including its retrospective design and the relatively small study population. Thus, larger prospective studies are needed to confirm our results and establish effective treatment protocols for such patients in order to improve their outcomes.

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