Original Article

Clinical features of organizing pneumonia associated with rheumatoid arthritis

Harutsugu Okada[1], Kazuhiro Kurasawa[1,2], Ryutaro Yamazaki[1], Ayae Tanaka[1], Satoko Arai[1], Takayoshi Owada[1], Reika Maezawa[1,2],and Yoshiki Ishii[1]

[1]Pulmonary Medicine and Clinical Immunology and [2]Center for Rheumatic Diseases, Dokkyo Medical University, Tochigi, Japan

Short title: Organizing Pneumonia in RA

Corresponding Author: Kazuhiro Kurasawa, MD
Center for Rheumatic Diseases, Dokkyo Medical University
880 Kita-Kobayashi, Mibu, Tochigi 321-0293, Japan
Tel: +81-282-87-2151
Fax: +81-282-86-5080
E-mail: kurasawa@dokkyomed.ac.jp

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Abstract

Objectives: To clarify the clinical features of organizing pneumonia (OP) associated with rheumatoid arthritis (RA) and to determine whether development of OP is related to RA activity.

Methods: For prevalence examination, medical records of 449 consecutive RA patients were reviewed. For clinical feature analysis, 24 patients with OP (19 from the prevalence examination and 5 additional) were enrolled. OP was diagnosed by pathological findings by trans-bronchial biopsy or by clinical features (typical computed tomography findings, no causative agents, good response to glucocorticoids, and lack of response to antibiotics).

Results: Among 499 patients, OP was found in 19 patients and the estimated prevalence was 1.9-4.8%. No differences in clinical features were noted between the OP and non-OP groups. In 24 OP patients, the mean age of OP development was 60.4 years and the period from onset of RA to OP ranged from -4 to +34 years. Although 18 patients presented OP after the onset of RA, 3 developed OP before RA and 3 developed OP simultaneously with RA. Patients receiving tumor necrosis factor inhibitors also developed OP. RA disease activity just before onset of OP was low in 10 of 18 RA cases. At the onset of OP, only 2 patients showed exacerbations of arthritis, while most patients

presented with fever and serum CRP elevations. Glucocorticoids were effective for OP in all patients who received them. Relapse occurred in 2 of 24 cases.

Conclusions: OP develops in approximately 4% of RA patients, which occurs independently from RA activity and at any time in RA patients.

Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory disease characterized by destructive polyarthritis. RA affects not only joints but also the organs. The lungs are one of the most commonly affected organs in RA, and the lung involvement in RA results in various clinical features including airway disease, interstitial lung diseases (ILD), and organizing pneumonia (OP) (1,2).

OP, previously referred to a bronchiolitis obliterans with organizing pneumonia (BOOP), is a form of ILD characterized by the presence of buds of granulation tissue in bronchioles and the alveoli (3,4, 5). Presentation of OP usually starts with flu-like symptoms such as fever, malaise, fatigue, and cough, but occasionally it showed an isidenous onset (5,6,7). Radiographic features include patchy or diffuse consolidation with/without ground glass opacities that frequently resemble bacterial pneumonia and tumors; lung biopsy is recommended to confirm the diagnosis (7-10). Cases may resolve spontaneously, although most patients require treatment; antibiotics are not helpful whereas glucocorticoids are an effective treatment option (5,7). There are two types of OP: cryptogenic OP and secondary OP (5,7,11). Secondary OP is associated with many entities such as infection, drugs, and connective tissue diseases (CTD) including RA

(7,11,12). However, clinical features of OP in RA patients remain unclear. In particular, it is not known whether the development of OP is related to RA disease activity, which is determined based on the status of arthritis.

The aim of the present study is to investigate prevalence of OP in RA and to clarify clinical features of OP associated with RA, and specifically, to determine whether the development of OP is related to RA disease activity.

Patients and Methods

Two cross-sectional studies were conducted; one for prevalence of OP and the other for analysis of clinical features of patients with OP.

Patients

In the assessment of prevalence of OP, a total of 499 consecutive Japanese patients with RA who visited Dokkyo Medical University hospital in December 2010 and met the American College of Rheumatology 1988 criteria for RA (13) were enrolled. Clinical features of OP were analyzed in 24 patients (19 were extracted from a prevalence asses, and 5 were admitted to our hospital because of OP from January 2011 to March 2013.

Pulmonary involvement was based on medical records and radiographic reports. All patients underwent chest radiography as a routine examination, and 340 of them underwent chest computed tomography (CT) scans which was performed on patients showing respiratory symptoms or abnormal findings on chest radiography, or receiving biologics. RA activity was judged by the Disease Activity Score-28/C-reactive protein levels (DAS28-CRP) based on three variables, tender joint counts, swollen joint_counts and serum CRP levels (14).

This study was conducted with the approval of the local ethics committee and according to Ethical Guidelines for clinical studies (2009) by Ministry of Education, Culture, Sports,

Science and Technology and Ministry of Health, Labour and Welfare, Japan.

Diagnosis of OP

OP was diagnosed when pathological findings of lung biopsy samples were compatible with OP or when patients fulfilled the following criteria: 1) typical pulmonary image findings (non-segmental randomized consolidation with/without ground glass opacities), 2) no causative infectious agents, and 3) no response to antibiotics and good response to glucocorticoid therapy which was judged by presence or absence of improvement of systemic and respiratory symptoms and chest infiltrate within 2 weeks. To exclude infection, microbiological examination of sputum and BALF (if possible) including mycobacterium and fungi, measurement of plasma β-D-glucan level, and tests for blood cytomegalovirus antigen and cryptococcal antigen were performed.

Analysis

Medical records of patients were reviewed retrospectively. Statistical analysis was conducted using JMP 7 software (SAS Institute Japan, Tokyo, Japan). All analyses were two-sided and the level of significance was set at $P<0.05$. For comparisons of two groups, Student's t-test, chi-square analysis, and the Mann-Whitney U-test were conducted. For multiple comparison analysis of proportions, chi-square analysis and analysis of variance were conducted.

Results

Prevalence of OP in RA

We first examined the prevalence of pulmonary diseases, including OP, in 499 consecutive RA patients through a review of medical records. Subjects included 133 males and 366 females with a mean age of 59.7 years and mean disease duration of 13.2 years, 74.6% of them were positive for RF and 31.8 % had a history of smoking.

Pulmonary involvement was observed in 188 of 499 RA patients (37.7%). OP was found in 19 cases (3.8%); and ILD other than OP, bronchial diseases (bronchiolitis, bronchiectasis), chronic obstructive pulmonary disease (COPD), and pleuritic diseases, were found in 13.0%, 4.8%, 3.5%, and 2.2%, respectively (Fig. 1). The estimated prevalence of OP was 1.9-4.8% (95% confidence interval) in RA patients.

Clinical features of patients with and without OP

Demographic and RA features of patients with OP, without OP, and without pulmonary involvement in December 2010 are shown in Table 1. No significant differences were found in characteristics between the OP and non-OP groups or the group without pulmonary involvement.

Characteristics of patients with OP

Further analysis of clinical features was conducted on 24 patients with OP including 19

patients from the above prevalence examination and additional 5 patients whom we experienced after the prevalence study (Table 2). OP was diagnosed by pathological findings on trans-bronchial lung biopsy (TBLB) samples in 14 patients; others were judged as having OP by clinical course with typical radiographic findings of OP, no causative pathogens, and good response to glucocorticoid therapy with no response to antibiotic therapy.

Patients with OP included 9 males and 15 females with an onset of RA at 49.6 ± 12.6 years (mean ± SD); 9 patients (37.5%) had a history of smoking. Rheumatoid Factor (RF) and anti-cyclic citrullinated peptide (CCP) antibody were positive in 16 (67%) and 19 (83%) patients, respectively. Six patients had pulmonary diseases before the onset of OP (ILD, 2; bronchiectasis, 2; COPD, 1; bronchiolitis, 1; and cystic pulmonary lesions, 1).

Time relation between onset of OP and RA

Ages at onset of RA and OP were 49.6 ± 12.6 and 60.4 ± 9.6 years, respectively (Table 2). The time periods from the onset of RA to OP ranged from -4 to +34 years (mean, 10.8 years and median, 6.0 years) (Fig. 2). Most patients (n=18; 75%) developed OP after the onset of RA; however, OP preceded RA in 3 (12.5%) of patients and occurred simultaneously with RA in 3 (12.5%) of patients.

Medications for RA at onset of OP

Eighteen patients who developed OP after the onset of RA received medications at the onset of OP; 14 patients were treated with methotrexate (mean dose, 8.0 ± 2.7mg), 13 with glucocorticoids (mean dose, 5.0 ± 2.5mg), 3 with sulfasalazine, and 8 with biologics (infliximab, 1; etanercept, 5; and adalimumab, 2).

Suspected causes of OP

In four cases, drug-induced OP was initially suspected to be triggered by drugs (adalimumab, two; etanercept, one; and bucilamine, one), because these agents were administered within 3 months before the onset of OP. However, these patients were re-administered the same suspected drug after improvement of OP, and they did not re-develop OP. In these cases, drugs were unlikely to have caused OP.

In one case, bacterial pneumonia preceded the development of OP. Symptoms and chest infiltration were partially improved with antibiotics, but still continued. Bronchoscopic examination was performed and samples obtained by TBLB revealed findings compatible with OP. Glucocorticoid therapy improved symptoms. This case could be considered post-infectious OP.

RA activity just before the onset of OP

Among the 18 patients who developed OP after the onset of RA, RA disease activity that was measured by DAS28-CRP(3) within 1 month before the onset of OP was high in

4 patients, moderate in 4 patients, low in 8 patients, and in clinical remission in 2 patients. Serum CRP levels before the onset of OP were 2.9 ± 5.2 mg/dl, the median of which was 0.56 mg/dl, and only 3 of 18 patients (17%) had serum CRP levels above 1.0 mg/dl. OP developed even in patients whose RA disease activity was well controlled.

Arthritis at the onset of OP

OP developed without exacerbation of arthritis in many cases (Table 2, Fig. 1). Exacerbation of arthritis was found in only 2 of 18 (11%) patients with pre-existing RA. Three patients who developed OP and RA simultaneously showed new onset arthritis.

Clinical manifestations at the onset of OP

At the onset of OP, 19 of 24 (79%) patients presented with fever and 15 (62.5%) had respiratory symptoms such as cough and dyspnea (Table 2). Serum CRP levels were elevated in most cases, regardless of the presence or absence of arthritis; the mean and median CRP levels were 10.66 ± 7.87 and 10.3 mg/dl, respectively, and 21 (88%) of patients showed serum CRP levels above 1.0 mg/dl.

Radiographic studies

Consolidation/alveolar opacities were found in 24 of 24 patients (100%) on high-resolution CT scan (HRCT). Ground grass opacities and reticular shadows were found in 9 (37.5%) and 2 of cases, respectively. Multiple consolidation was detected in 18

(75%) and bilateral lung infiltration was seen in 9 (37.5%) of the patients. These alveolar opacities/ consolidation were frequently found in middle and lower lung zones. Spontaneous disappearance of OP occurred in 8 (33%) of patients. Pleural effusion was found in 3 (12.5%) of OP cases.

Response to antibiotics and glucocorticoid therapy

Antibiotics were given to 13 patients; however, only 1 patient responded to the therapy. As described above, this patient had initially suffered from bacterial pneumonia and partially responded to antibiotics; follow-up treatment with glucocorticoid therapy completely resolved the OP. In contrast to antibiotics, glucocorticoid (0.8 mg/kg-1.0 mg/kg), which was administerated to 16 patients, was effective in all cases and resolved symptoms and radiographic abnormalities completely.

Relapse of OP and prognosis

When OP was resolved, the dose of GC was tapered and DMARDs or biologics were restarted. Relapse of OP occurred in 5 of 24 patients (21%) (Table 2). The duration between onset and relapse of OP was 3 months to 14 years (mean, 3.3 years; median, 1.7 years). Multiple relapses occurred in 2 patients. One patient had multiple relapses after induction of therapy with tocilizumab that controlled arthritis well.

Among 24 patients with OP, three patients died by the end of 2014 (mean observation

period from onset of OP, 6.7 years). Causes of death were lung cancer in one, chronic heart failure in one, and exacerbation of preexisting usual interstitial pneumonia (UIP) in one.

Discussion

In the present study, we showed clinical features of OP associated with RA. We found the following: 1) OP is not uncommon in patients with RA, 2) OP can develop at any time in patients with RA, although many cases occurred after the onset of RA, 3) OP development is not associated with RA disease activity, 4) OP emerges even in patients receiving biologic agents, such as tumor necrosis factor (TNF) inhibitors, and 5) OP responds well to glucocorticoids, although relapses occasionally occur. The present study was the first a cross-sectional retrospective review showing clinical features of OP in patients with RA, although many cases of OP associated with RA have been reported.

The present study showed that approximately 4% of patients with RA experienced OP during RA courses. The prevalence of OP in the general population remains unknown. The cumulative prevalence of OP from Canada was reported to be 12.0/100,000 admissions in general population (15). The mean annual incidence of OP in general population was reported at 1.97/100,000 in Iceland (16) In the present study, given that

the observation period was 14 years during which patients had RA, the annual incidence was of OP estimated to be 272/100,000 (0.03%). The prevalence and annual incidence of OP in RA in this study was larger than in the general population. Other studies have shown that OP was found in 6 of 40 (15%) cases and 5 of 54 (9%) cases with RA-ILD who received surgical lung biopsy (17, 18). Tanaka et al also reported that 5 of 63 (8%) patients with RA-ILD had OP patterns on HRCT imaging (19). Taken together, the prevalence of OP in RA is greater than that in the general population and RA-associated OP is not uncommon.

The present study showed that OP occurred after the onset of RA in most cases, but some patients developed OP simultaneously with or before the onset of RA. There have been reports about OP that simultaneously developed with RA (20) or cases in which OP preceded RA (21,22). Consistent with our results, Mori et al summarized case reports about OP in RA and showed that 21, 4, and 1 cases developed OP after, before and simultaneously with the onset of RA, respectively (20). Yoo et al also reported that 4 and 3 cases of RA-OP, in which pulmonary lesions developed, occurred after and simultaneously with the onset of RA, respectively (12).

We demonstrated that OP development is not associated with RA activity that is determined clinically. There have been reports that OP developed in both patients with

and without active arthritis (23-25). Unfortunately, most of reports about OP in RA did not describe RA activity at the onset of OP. Therefore it remained unclear whether OP development was associated with RA activity.

Mori et al reviewed cases of OP in RA and described that there might be a strong relationship between OP and RA disease activity (20). However, the relationship that the authors claimed was based on the following: 1) most cases were positive for RF; 2) some cases developed OP with increasing titers of RF; and 3) OP occurred in two patients when arthritis was worsening. We consider that these data indicate the relationship of the development of OP with immunological abnormality rather than RA disease activity itself.

The present study showed for the first time that OP development is not associated with RA activity. This finding indicates that physicians should suspect OP in patients with RA when chest infiltrates develop even when RA disease activity is not present. In addition, this finding suggests that the mechanism of the development of OP might differ from that of arthritis, although there might be shared background of immunological abnormalities in RA as suggested by Mori et al (20). This idea could also be supported by cases in which OP preceded the onset of RA and cases of OP that developed when RA was under good control.

It is well known that OP can be induced by drugs, including biologics (5,7,25-27). In the present study, TNF inhibitors, which controlled arthritis well, were first suspected to have induced OP in several patients who had recently started treatment with these agents. However, this possibility was unlikely, because these patients were retreated with the same agents and did not show any signs of OP. This finding suggests that OP developed independently from the TNF-mediated pathway that induced arthritis in these patients.

Clinical features of secondary OP in RA in this study were similar to those of cryptogenic OP in presentation, symptoms, and imaging (5-8), which was consistent with a report by Yoo et al that the clinical features of connective tissue disease-related OP were similar to cryptogenic OP (12). In the present study, glucocorticoids were effective and resolved OP in all cases, although there have been reports of glucocorticoid-resistant and/or fatal cases of OP in RA (24, 28). Mori et al reported that 5 of 26 cases of OP in RA were glucocorticoid-resistant and one case was fatal in their literature review (20). Yoo et al showed that patients with connective tissue disease-OP (CTD-OP) had a lower complete recovery rate when compared with patients with cryptogenic OP (12). These resistant or fatal cases might have had other ILD components such as non-specific interstitial pneumonia (NSIP) in addition to OP, and might suffer from acute fibrinous

and organizing pneumonia, a new form of acute/subacute lung injury mimicking OP (29).

Relapse was observed in 20%of patients in the present study. Mori et al reported relapse in 1 of 26 cases (20). Yoon et showed that CTD-OP had a tendency towards higher recurrence compared with cryptogenic OP (12).

The present study has several limitations. One is a small number of cases of OP. We failed to find differences in clinical features, including RF titers, between patients with and without OP. Mori et al suggested OP cases had high immunological activities such as increasing/high RF titers. A larger number of cases is needed to confirm these findings. The other limitation was that 10 of 24 cases (42%) were diagnosed as having OP by only clinical features, and not by histologic findings, although no differences in clinical features were found between patients with and without OP (data not shown). In the other 14 cases, samples for histological examination were obtained by TBLB, not by surgical biopsy. Thus, we would not rule out the possibility that cases diagnosed as OP in the present study might be an ILD other than OP, as ILD in CTD frequently have combined histologic patterns. However, the present study demonstrated clinical features of OP associated with RA, particularly no relationship of OP onset with RA activity.

In conclusion, OP is a common pulmonary complication that can develops independently from RA activity and at any time in patients with RA. Physicians treating patients with

RA should consider OP when chest infiltrates are shown on imaging studies.

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Figure legends

Fig.1.Prevalence of pulmonary involvements in RA

Total 499 RA patients were examined for existence of pulmonary involvement including history of organizing pneumonia through reviewing medical records.
Bronchial Dis; (bronchial diseases (bronchiolitis, bronchiectasis) , COPD; Chronic Obstructive Pulmonary Disease, ILD; interstitial pneumonia, NTM; nontuberculous mycobactelial infection, OLD INF; old pulmonary inflammatory lesions (inflammatory nodules and/or scars), OP; organizing pneumonia, PE; pleural effusion.

Fig.2. Interval from the onset of RA to organizing pneumonia (OP)

Symbols indicate the onset of OP. Closed symbols indicate cases with exacerbation/ new onset of arthritis. Open symbols indicate cases without exacerbation of arthritis.