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CASE REPORT

A simultaneous onset of organizing pneumonia and rheumatoid arthritis, along with a review of the literature

Shunsuke Mori · Isamu Cho · Yukinori Koga · Mineharu Sugimoto

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Abstract Organizing pneumonia (OP) is a specific type of interstitial pneumonia that has been noted as one of the pulmonary manifestations during the course of rheumatoid arthritis (RA). In this study, we report a case with a simultaneous development of OP and RA. The patient presented with concurrent flu-like symptoms and arthralgia of multiple joints, and antibiotic therapy was not effective. The rheumatoid factor (RF) and anti-cyclic citrullinated antibodies were both high. Multiple air-space opacities on chest radiographs and bilateral peripheral consolidations on high-resolution computed tomography films were evident. The histology of transbronchial lung biopsy samples was characterized by intra-alveolar buds of granulation tissue consisting of intermixed myofibroblasts and connective tissues. Treatment with prednisolone induced a complete recovery from OP without relapses. Our review of previous reports about RA-associated OP (RA-OP) suggested that the high titer of RF and increased disease activity of RA indicate a great risk of developing OP. This condition may represent a lung's reaction in the RA-associated inflammatory and/or immune process. We should be aware of RA-OP cases in which pulmonary manifestations precede articular symptoms. In these cases, respiratory manifestations are the main evidence of RA activity. In most cases of steroid-resistant RA-OP, the use of immunosuppressants was effective. Since OP may progress to fibrotic lung disease during the course of RA, we may consider performing a second lung biopsy for steroid-resistant patients, even if they have once been diagnosed as OP.

Keywords Bronchiolitis obliterans with organizing pneumonia · Interstitial pneumonia · Organizing pneumonia · Rheumatoid arthritis · Rheumatoid factor

S. Mori (✉)
Clinical Research Center for Rheumatic Disease and Department of Rheumatology, Kumamoto Saishunsou National Hospital, 2659 Suya, Kohshi, Kumamoto 861-1196, Japan
e-mail: moris@saisyunsou1.hosp.go.jp

I. Cho
Clinical Research Center for Rheumatic Disease and Division of Respiratory Medicine, Department of Medicine, Kumamoto Saishunsou National Hospital, Kumamoto, Japan

Y. Koga
Clinical Research Center for Rheumatic Disease and Department of Radiology, Kumamoto Saishunsou National Hospital, Kumamoto, Japan

M. Sugimoto
Division of Respiratory Medicine, Department of Medicine, Kumamoto Saishunsou National Hospital, Kumamoto, Japan

Introduction

Organizing pneumonia (OP) is a clinicopathological syndrome that has a long and complicated history. In 1983, Davison et al. [1] first described a group of patients with OP, but with no evidence of an infective or other causative agent, and they introduced the term of cryptogenic organizing pneumonia (COP). In 1985, Epler et al. [2] provided a classic description of the same disease under the term of bronchiolitis obliterans with organizing pneumonia (BOOP). Since then, OP has been noted in association with a variety of clinical conditions, such as infections, drugs, radiotherapy, and connective tissue disorders (secondary OP) [3, 4]. In 2002, the American Thoracic Society/European Respiratory Society (ATS/ERS) recommended that the term of COP be used for idiopathic cases, emphasizing the cryptogenic nature of the disease process. Recently, the term OP has been

preferably used because the major pathological feature of this condition is OP and the bronchiolitis obliterans is only a minor and accessory finding or may not be present in tissue samples [3–8]. Besides, the use of BOOP may cause diagnostic confusion with other airway diseases, bronchiolitis obliterans of the constrictive type, for example.

OP, whether cryptogenic or secondary, is histologically characterized by intra-alveolar buds of granulation tissue consisting of myofibroblasts and fibroblasts embedded in connective tissue [6, 7, 9]. These buds extend into the alveolar ducts and spaces (OP pattern) and also fill bronchiolar lumens (bronchiolitis obliterans of the proliferative type). As mentioned above, the OP pattern is usually most prominent, but the latter may be minor. Lymphocytic interstitial inflammation with mononuclear cells is present in areas of OP, but usually mild. An accumulation of foamy macrophages may be present in alveolar spaces. The most interesting characteristic of intra-alveolar organization in OP, especially COP, is its reversibility in response to steroid therapy [4, 8, 10, 11]. In this respect, OP is distinguished from other irreversible lung fibrosis, such as idiopathic pulmonary fibrosis, and also from the bronchiolitis obliterans of the constrictive type associated with irreversible obstructive lung diseases.

OP has been reported as one of the pulmonary manifestations of rheumatoid arthritis (RA) [8, 12, 13]; however, a relationship between OP occurrence and RA disease activity remained an unanswered question. The steroid responsiveness of RA-associated OP (RA-OP) is still controversial. In this study, we describe clinical, histological, and radiographic features of a case of OP that developed simultaneously with the onset of RA. We also review 25 cases of RA-OP in the literature published from 1987 through 2006.

Case report

A 45-year-old non-smoking woman was admitted to our hospital because of antibiotic-refractory pneumonia. Three weeks earlier, she had consulted a doctor in her neighborhood about flu-like symptoms, such as high fever and nonproductive cough without dyspnea. Simultaneously, she had complained of arthralgia of multiple joints. A chest radiograph taken at that time revealed a consolidation in the upper lobe of the left lung. The patient had been treated with an antibiotic (clarithromycin), but her clinical condition was getting worse and multiple consolidations appeared in the upper and middle lobes of the right lung, as well as in the upper lobe of the left lung. Since a significant increase in serum levels of IgA and IgG antibodies (Abs) against Chlamydia pneumoniae (the TWAR agent) was noted, the oral administration of clarithromycin was replaced with a drop infusion of ciprofloxacin hydrochloride. Neither serum anti-mycoplasma IgM Ab nor urine pneumococcal antigen nor urine Legionella antigen was detected. Despite the treatment with antibiotics for a period of 3 weeks, her respiratory symptoms or radiological abnormalities had not improved, and the joint pain had deteriorated.

On admission, the patient complained of nonproductive cough and pain of multiple joints, and a physical examination showed swelling and tenderness of the proximal interphalangeal (PIP) joints of the third and fourth fingers in both hands and bilateral wrist joints. The patient's body temperature was 38.9°C and oxygen saturation by pulse oximetry was 95%. Inspiratory crackles were audible in both lung fields. Laboratory findings showed elevated levels of erythrocyte sedimentation rate (ESR, 139 mm/h) and C-reactive protein (CRP, 25.1 mg/dl). White blood cell count was 13,210 per microlitres and neutrophils were dominant (79.7%). Liver enzymes were slightly increased (aspartate aminotransferase, 27 IU/ml; alanine aminotransferase, 46 IU/ml), and the other data on blood biochemistry were within normal ranges. Serological findings were as follows: antinuclear antibody, negative; IgM rheumatoid factor (RF), 294 IU/ml; anti-cyclic citrullinated antibodies (anti-CCP Abs), more than 100 U/ml; C_3, 154.2 mg/dl; C_4, 16 mg/dl. Serum levels of interstitial markers, KL-6 and SP-D, were both within normal levels.

Chest X-ray films showed multiple patchy infiltrates on both lung fields (Fig. 1) and high-resolution computed tomography (HRCT) revealed alveolar infiltrative opacities with bilateral peripheral consolidations (Fig. 2). These findings were reminiscent of OP. The histology of transbronchial lung biopsy (TBLB) samples showed intra-alveolar buds composed of granulation tissues and interstitial infiltration of mononuclear cells (Fig. 3). In an analysis of bronchoalveolar lavage (BAL) fluids, CD4/CD8 ratio was 1.8 and cellular patterns of lymphocytic alveolitis were observed, but no evidence of infection was obtained. All the findings of TBLB and BAL were consistent with the main features of OP.

Because OP was suspected, we started steroid pulse therapy (intravenous injection of methylprednisolone, 1 g daily, three times), followed by 40 mg/day of oral prednisolone. The patient promptly responded to the steroid therapy. One month later, the radiographic abnormalities were completely improved and her flu-like symptoms had cleared up. Recurrences had not occurred upon reducing prednisolone. Since at this point the patient fulfilled at least four criteria listed in the 1987 ACR criteria for the classification of RA, we finally made a diagnosis of RA-OP. After the clinical and radiographic improvement, we introduced 6 mg/week of methotrexate (MTX) for RA. The RA activity was suppressed during the steroid therapy for OP, but the

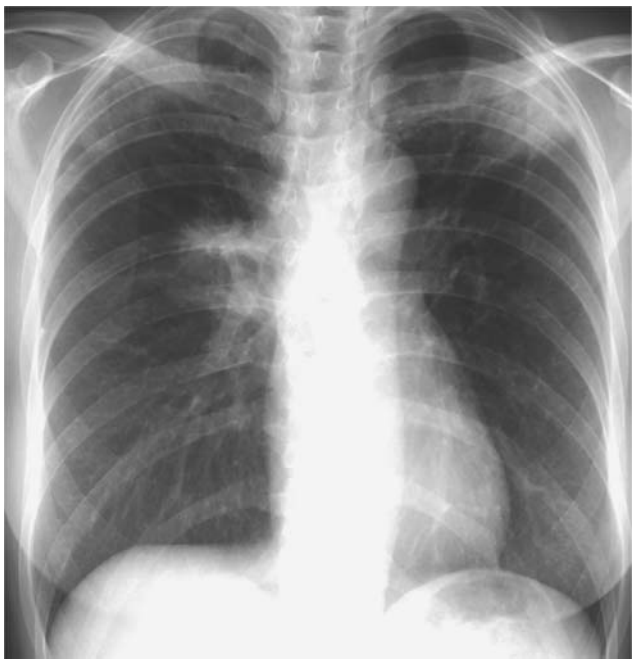

Fig. 1 A chest radiograph shows patchy air-space opacities in the upper lobe of the left lung and in the upper and middle lobes of the right lung

articular symptoms took a turn for the worse as prednisolone was tapered off. We therefore continued 15 mg/day of prednisolone. Two months after admission, the patient had ten swollen and 16 tender joints, and the visual analog scale was 86 mm. The RF titer was markedly increased (664 IU/ml), and HAQ score was 2.5. Despite MTX therapy for 2 months, her articular symptoms did not improve. Currently, the patient is being treated with 6 mg/week of MTX and 15 mg/day of prednisolone under monitoring for symptomatic and radiographic signs of OP, and we are considering an introduction of infliximab therapy.

Discussion

OP is considered as a specific type of interstitial pneumonia, and its association with RA has been reported [8, 12–14]. In a series of 40 patients with RA undergoing open lung biopsy, OP was the second most common primary histological pattern [15]. As a rule, rheumatoid lung diseases occur more frequently in men who have long-standing rheumatoid disease and positive RF [14]; however, little is known about whether a risk of OP occurrence may be related to the disease activity of RA. In this study, we reported a female patient who had presented articular manifestations and flu-like respiratory symptoms simultaneously. Her disease was active and RF titers were relatively high at onset. For further understanding of RA-OP, we reviewed 25 cases in the literature from 1987 through 2006 [8, 11–13, 16–31] and summarized the clinical features in Table 1, including RF titers, RA duration, treatments for RA and OP, and clinical outcomes. Some cases were excluded because information about RF titers or other disease activity parameters was not provided. Some cases that had been diagnosed as anti-RA drug-induced OP by authors themselves were also excluded. Our case is included in Table 1 as case 26. Among 26 cases, 18 were Japanese. The mean age of all patients was 57 years, and ranged from 24 to 75. The ratio of male to female was 11 to 15. In most cases, OP developed during the course of RA, and articular symptoms preceded pulmonary manifestations. The period from RA onset to OP occurrence varied, ranging from 4 months to 30 years. In our case, both conditions were observed simultaneously. Of note, in three cases OP preceded the clinical onset of arthritis about 2 weeks (case 3), 1 month (case 2), and several months (case 1), respectively. In case 4, the RAHA in pleural effusion was 1:640, but articular symptoms were not yet observed. Thus we should bear in mind that in some RA cases, pulmonary manifestations are the main evidence of disease activity.

As shown in Table 1, most cases had positive RF or RAHA, and only 4 (15%) were negative. Ten cases showed a remarkably high titer of RF or RAHA at the onset or during the course of OP (more than 1,000 IU/ml of RF or more than 1:1,000 of RAHA), and three cases had a relatively high titer of RF or RAHA (more than 300 IU/ml of RF or more than 1:300 of RAHA). Our case also had a relatively high titer of RF. One (case 8) showed an increased level of MMP-3, a recently reported parameter of disease activity. In particular, the titers of RF or RAHA in five cases were markedly increased in association with the progression of OP (cases 3, 5, 6, 12, and 15). A high titer of RF may indicate a great risk of developing OP in RA patients. Recent reports showed that RF is the strongest predictor of radiographic progression in RA [32]. A further value may be in predicting OP development. In two cases, OP occurred concomitantly with a flare-up of articular symptoms (cases 9 and 15). Case 20 showed a simultaneous onset of OP and pernicious anemia, an autoimmune disease. All the findings support the idea that OP is a pulmonary reaction in the inflammatory and/or immune process associated with the underlying condition, and there is a strong relationship between OP and the disease activity of RA.

COP has been reported to respond to corticosteroids with a complete resolution of clinical symptoms and radiographic findings. Patients with secondary forms of OP also have good outcomes; however, some cases in patients with RA may be resistant to steroid therapy [33–35]. Cohen et al. [34] reported two RA cases with rapidly progressive

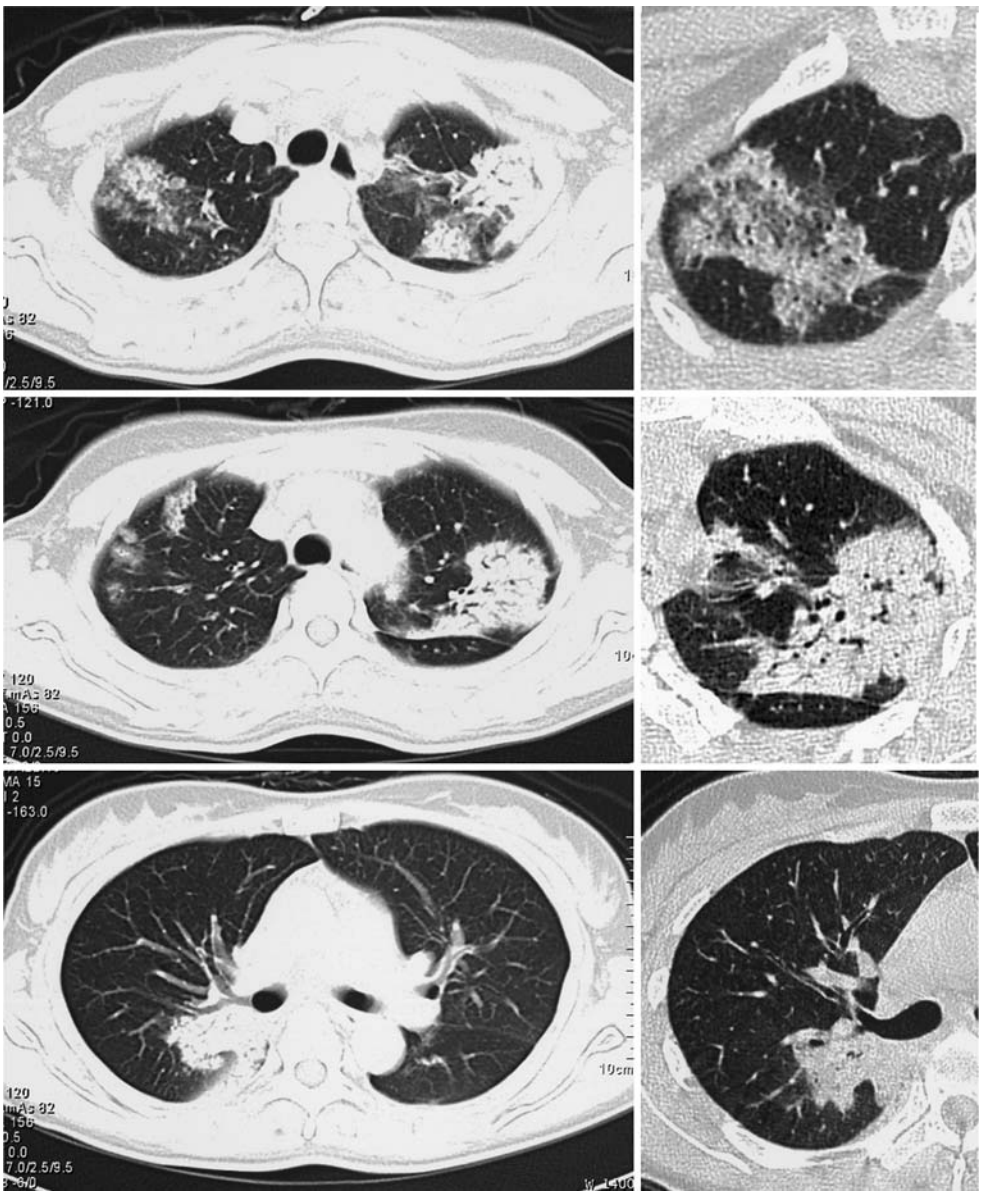

Fig. 2 HRCT shows bilateral patchy areas of consolidations in the peripheral subpleural regions

OP that had resulted in severe respiratory failure and death. The patients had characteristic histological findings of OP, but at autopsy the predominant histological pattern was alveolar septal inflammation and interstitial fibrosis with honeycombing. These findings suggest a development of nonspecific interstitial pneumonia (NSIP) or usual interstitial pneumonia (UIP). OP may have progressed to steroid-resistant fibrotic lung disease in a chronic inflammatory process associated with active RA. Therefore we may not hesitate to perform lung biopsy repeatedly when we encounter steroid-resistant patients, even if they have once been diagnosed as RA-OP. As shown in Table 1, most cases responded rapidly to steroid therapy. Two cases of interest achieved complete remission simply with an intra-articular injection of steroid (cases 10 and 20), which was done for a treatment of arthritis. In cases 7 and 25, prednisolone was effective, but a recurrence was observed upon a tapering off of steroids. Four cases were resistant to steroid therapy (cases 1, 4, 8, and 18). Whether the mixed patterns of interstitial lung disease may be present in these cases is unknown. Alternative treatment with cyclosporine or cyclophosphamide was introduced for them. Four cases were improved (cases 4, 7, 8, and 18), but case 7 finally died of a fatal stroke. Case 1 was resistant to the combination therapy of steroid and cyclosporine and died. Assuming that RA-OP may represent the lung's inflammatory response related to the RA activity, the use of immunosuppressants for steroid-resistant OP appears to be

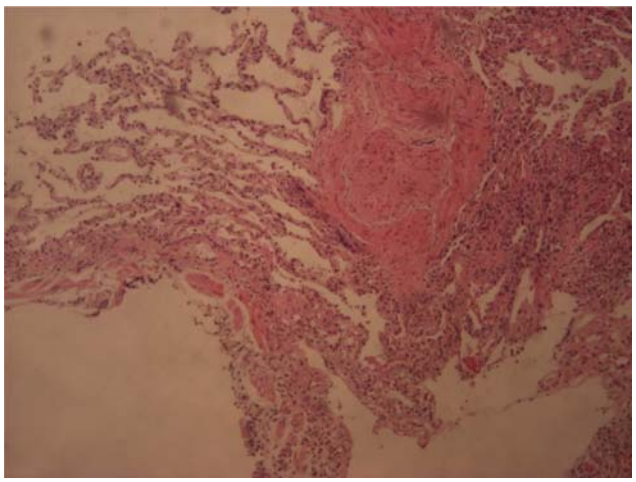

Fig. 3 A histological examination of TBLB specimen shows intra-alveolar buds of granulation tissue consisting of intermixed myofibroblasts and connective tissues. Interstitial infiltrates of mononuclear cells are seen (HE staining, ×100)

rational. Our case showed a complete recovery from OP without relapses. Her TBLB data indicated the typical histological pattern of OP, and until now we have obtained no evidence about progression to fibrotic lung disease.

Several disease-modifying anti-rheumatic drugs (DMARDs) have been reported to cause iatrogenic OP. Most recently, drug-induced OP was shown in patients with RA under treatment with bucillamine (an analog of D-penicillamine) [36, 37] and sulfasalazine [38]. MTX- or gold-induced OP was also reported in other clinical conditions [4]. These findings suggest that the pathogenesis of OP is more complicated in RA patients receiving DMARDs than in those without RA therapy. As shown in Table 1, seven cases had an experience of receiving one or two DMARDs. Since clinical features and radiographic findings are similar between patients with OP, both derived from RA per se and related to RA treatment, a causal relationship seems to be established only by the resolution

Table 1 Clinical characteristics of patients with RA-associated OP

Case no.	Age/sex	RF or RAHA (disease activity)	DMARDs	RA duration at OP onset	Treatment	Outcome	References
1	74/M	(2+)	None	Preceded	Pred CYA	Resistant died	[16]
2	55/F	16 IU/ml or 1:640	None	Preceded	Pred	R	[17]
3	68/F	1:640 to 1:1,280	None	Preceded	Pred	R	[11]
4	49/F	(1+) or 1:160	None	Preceded	m-Pred CTX	Resistant R	[18]
5	45/F	(−) to 1:2560	None	4 months	Pred	R	[8]
6	75/M	1:160 to 1:1,280	HCQ	11 months	Pred	R	[12]
7	75/M	(1+)	HCQ	15 months	Pred CTX	Relapsed R	[19]
8	61/M	(MMP-3, 286 ng/ml)	Buc/MTX (steroid)	2 years	Pred CYA	Resistant R	[20]
9	34/F	2,450 IU/ml (flare-up)	CTX (steroid)	2 years	Pred	R	[21]
10	54/M	(2+)	None	2 years	Pred i.a.	R	[22]
11	24/F	(−)	None	2 years	Pred	R	[23]
12	52/F	1:2,560 to 1:5,120	D-Pen/gold	5 years	Pred	R	[8]
13	59/M	1:1,280	(Steroid)	5 years	Pred	R	[24]
14	56/M	(2+) or 1:2,560	None	6 years	Pred	R	[25]
15	58/F	364 to 1,460 IU/ml (flare-up)	(Steroid)	7 years	Pred	R	[26]
16	62/F	494 IU/ml	D-Pen	7 years	Pred	R	[27]
17	66/M	1,340 IU/ml	(Steroid)	7 years	Pred	R	[28]
18	56/M	(−)	AZA	18 years	Pred CTX	Resistant R	[29]
19	53/F	(1+)	(Steroid)	19 years	Pred	R	[13]
20	72/F	(2+) or 1:1,280 (malignant anemia)	None	22 years	m-Pred i.a.	R	[30]
21	59/F	1:320	None	30 years	Pred	R	[8]
22	58/M	(1+)	ND	Chronic RA	Pred	R	[31]
23	59/F	(−)	ND	Chronic RA	Pred	R	[31]
24	42/F	(−)	ND	Chronic RA	Pred	R	[31]
25	57/M	(2+)	ND	Chronic RA	Pred	Relapsed	[31]
26	45/F	294 IU/ml	None	Simultaneously	Pred	R	Mori

CTX cyclophosphamide, *Buc* bucillamine, *Pred* prednisolone, *m-Pred* methyl-prednisolone, *HCQ* hydroxychloroquine, *D-Pen* D-penicillamine, *AZA* azathioprine, *CYA* cyclosporine, *i.a.* intra-articular injection, *R* recovered, *ND* not described

of OP following the discontinuation of suspected drugs. However, it may be difficult to decide on a discontinuation of DMARDs. Upon stopping DMARDs, the disease activity of RA may be increased and thereby pulmonary manifestations of OP may go from bad to worse.

In conclusion, OP is sometimes observed during the course of RA as one of the pulmonary involvements; however, in some cases, respiratory manifestations are the main evidence of RA activity. We should recognize the OP cases simultaneously developing or preceding articular symptoms. OP appears to be an inflammatory reaction of lung that is associated with RA activity, and the high titer of RF may be related to a great risk of developing OP. The prognosis for RA-OP is usually satisfactory, but some cases may progress to steroid-resistant fibrotic lung disease. A lung biopsy should be done early if OP is suspected. Furthermore, we may consider making lung biopsies again for steroid-resistant patients, even if the first histological examination yields a diagnosis of OP.

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