Successful treatment of three patients with organizing pneumonia associated with rheumatoid arthritis using clarithromycin and prednisolone

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1. Introduction

Bronchiolitis obliterans organizing pneumonia (BOOP) was described in 1985 as a distinct entity, with different clinical, radiographic, and prognostic features, compared with obliterative bronchiolitis and the usual interstitial pneumonia/idiopathic pulmonary fibrosis (1). Most patients with the above features were diagnosed with idiopathic BOOP, now called cryptogenic organizing pneumonia (COP), but there are several known causes of organizing pneumonia (OP). One of the causes is collagen vascular disease, such as rheumatoid arthritis (RA), systemic lupus erythematosus and Sjogren’s syndrome. In addition, radiotherapy and some drugs are known to cause OP (2). In general, treatment for COP commonly includes corticosteroids (CSs) with or without another immunosuppressive agent. Macrolides have anti-inflammatory effects and have been used to treat diffuse panbronchiolitis, bronchiectasis, and cystic fibrosis (3-5). Several cases of COP and radiotherapy-related OP that were successfully treated with macrolides considering their anti-inflammatory effects were reported (6-9). Herein, we report three cases of OP associated with RA successfully treated with clarithromycin (CAM) and prednisolone (PSL).

Summary

Macrolides have anti-inflammatory effects and have been used to treat diffuse panbronchiolitis, bronchiectasis, and cystic fibrosis. Lately, several cases of cryptogenic organizing pneumonia (COP) and radiotherapy-related organizing pneumonia (OP) that were successfully treated with macrolides considering their anti-inflammatory effects were reported. We report three cases of OP associated with rheumatoid arthritis (RA) successfully treated with clarithromycin (CAM) and prednisolone (PSL). Case 1: A 70-year-old woman suffering from RA was admitted with cough and severe dyspnea. She was diagnosed with OP associated with RA on the basis of computed tomography (CT) findings and transbronchial lung biopsy results. She was successfully treated with PSL and cyclosporine A. At the exacerbation of OP, she was successfully treated with CAM and PSL. Case 2: A 74-year-old man suffering from COP visited our department with arthralgia and articular swellings. He was diagnosed with RA, which was thought to be associated with OP. He was successfully treated with CAM and PSL. Case 3: A 54-year-old man suffering from RA presented with an exacerbation of arthralgia and articular swellings and cough. He was diagnosed with OP associated with RA on the basis of CT findings. He was successfully treated with CAM and PSL. The present cases suggest that CAM and PSL treatment may be effective in some cases of OP associated with RA.

Keywords: Rheumatoid arthritis, organizing pneumonia, clarithromycin, prednisolone

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2. Case Report

2.1. Case 1

A 70-year-old woman was admitted with cough and severe dyspnea. She had been diagnosed with RA at 68 years of age and had been administered salazosulfapyridine (SASP). For 2 years, her general condition including arthralgia and articular swellings had been stable under this treatment. On this admission, coarse crackles were heard in bilateral lower lung fields. Laboratory findings were as follows: white blood cell (WBC) count, 6,430/μL (neutrophils, 61.1%; lymphocytes, 25.7%); aspartate aminotransferase level, 33 IU/L; alanine aminotransferase level, 25 IU/L; lactate dehydrogenase (LDH) level, 366 IU/L (normal range, 115-245 IU/L); C-reactive protein (CRP) level, 1.07 mg/dL; and rheumatoid factor (RF), 5 IU/mL (normal value, < 15.0 IU/mL). The anti-nuclear antibody titer was 40× with a speckled pattern, and the anti-SS-A antibody was positive. Negative results were obtained for anti-SS-B, anti-RNP, anti-DNA, and myeloperoxidase anti-neutrophil cytoplasmic antibodies. Arterial blood gas analysis showed pH, 7.412; PaCO₂, 30.7 Torr; PaO₂, 55.8 Torr; and HCO₃⁻, 22.1 mmol/L. Chest roentgenogram showed interstitial shadows in bilateral lower lung fields. Chest computed tomography (CT) revealed airspace consolidation and ground-glass opacity with a peribronchovascular distribution in bilateral lung fields on admission. Chest CT revealed considerable improvement of organizing pneumonia (OP) shadows 1 month after prednisolone (PSL) (40 mg/day) treatment. High-resolution CT revealed non-exacerbated OP shadows on PSL (5 mg/day) treatment. High-resolution CT reveals further improvement in OP shadows 6 months after PSL (8 mg/day) treatment.

Figure 2. Lung biopsy specimen. Lung biopsy specimen reveals intra-alveolar organization, alveolar thickening, and mononuclear cell infiltration (H&E stain, 100×).
PSL (40 mg/day) in combination with cyclosporine A (CyA) (100 mg/day). One month after initiating this treatment, chest CT revealed considerable improvement of OP shadows (Figure 1B). The PSL dosage could be gradually reduced to 5 mg/day over 7 months. On the other hand, CyA could be discontinued in 19 months. OP shadows had been stable under PSL in combination with CyA treatment and subsequent PSL (5 mg/day) treatment. At 72 years of age, OP shadows exacerbated on PSL (5 mg/day); therefore, the PSL dosage was increased to 20 mg/day. Because OP shadows gradually improved, the PSL dosage could be gradually decreased again to 5 mg/day without an exacerbation of OP shadows on high-resolution CT findings (Figure 1C). The long-term use of PSL induced diabetes mellitus and osteoporosis. At 78 years of age when the PSL dosage was 5 mg/day, OP shadows on high-resolution CT findings worsened (Figure 1D). Laboratory findings were as follows: WBC count, 5,600/µL (neutrophils, 60.3%; lymphocytes, 24.5%); LDH level, 237 IU/L; and CRP level, 0.56 mg/dL. Instead of increasing the PSL dosage, we added CAM (800 mg/day) to PSL (5 mg/day) considering its anti-inflammatory effects. One month after initiating CAM, a slight improvement was found in OP shadows on high-resolution CT findings, with CRP level decreasing to 0.30 mg/dL (Figure 1E). Because the patient complained of severe diarrhea, CAM was ceased. The PSL dosage was increased to 8 mg/day. Six months after initiating PSL (8 mg/day), OP shadows on high-resolution CT findings further improved slightly (Figure 1F).

2.2. Case 2

A 74-year-old man suffering from COP visited our department with arthralgia accompanied by partial swellings of proximal interphalangeal and metacarpophalangeal joints with morning stiffness. COP was diagnosed at another hospital 2 months before the episode of articular symptoms during a routine examination of his chest roentgenogram for hypertension. Because the patient did not complain of respiratory symptoms, he did not receive any treatment at the time. On this visit to our department, a slight fine crackle was heard in the right lower lung field. Laboratory findings were as follows: WBC count, 6,280/µL; CRP level, 6.05 mg/dL; and RF, 83 IU/mL. Bone roentgenogram revealed periarticular osteopenia in the bilateral knees and wrist joints. High-resolution CT revealed airspace consolidation and ground-glass opacity in the right lower lung field compatible with OP (Figure 3A). Because of symmetric polyarthritis of the small joints in both hands and feet along with morning stiffness and a positive RF, a diagnosis of RA was made according to the American College of Rheumatology criteria. It was thought that OP was associated with RA. Because the above-mentioned opacities gradually exacerbated, the patient was treated with PSL (5 mg/day) and CAM (400 mg/day) in combination with prednisolone (5 mg/day) treatment.

2.3. Case 3

A 54-year-old man suffering from RA presented with an exacerbation of arthralgia and articular swellings and cough. He had been diagnosed with RA at 45 years of age and had been administered SASP and subsequently SASP in combination with PSL (5 mg/day). His general condition including arthralgia and articular swellings had been stable under this treatment about for 1 year; however, arthralgia and articular swellings had worsened. SASP was changed to methotrexate (MTX) (6 mg/week), and his symptoms improved. At 47 years of age, the patient presented with an exacerbation of arthralgia and articular swellings and dyspnea. Chest
CT demonstrated pleural and pericardial effusions. The patient was diagnosed with pleuritis and pericarditis associated with RA. He was treated with methyl PSL (1 g/day) for 3 days and subsequently PSL (60 mg/day) in combination with cyclophosphamide (CPM) (100 mg/day). After pleuritis and pericarditis improved, the PSL dosage was gradually decreased to 5 mg/day over 3 years. On the other hand, CPM was ceased in 8 months. For about 4 years, his general condition including arthralgia and articular swellings had been stable under PSL (5 mg/day) treatment. On this visit, his laboratory findings were as follows: WBC count, 6,020/μL (neutrophils, 42.2%; lymphocytes, 27.9%); LDH level, 152 IU/L; and CRP level, 0.41 mg/dL. High-resolution CT revealed peculiar airspace consolidation and ground-glass opacity (reversed halo sign), compatible with OP (11) (Figure 4A). The patient was diagnosed with OP associated with RA. Because he was suffering from diabetes mellitus, the PSL dosage was increased from 5 mg/day to 10 mg/day only. Additionally, we prescribed CAM (800 mg/day) considering its anti-inflammatory effects. Three months after initiating CAM, OP shadows on high-resolution CT findings improved considerably (Figure 4B). CAM was ceased in 3 months and the PSL dosage could be gradually decreased to 5 mg/day over 4 months.

3. Discussion

In general, the treatment for COP commonly includes CSs with or without other immunosuppressive agents. CSs, with their potent anti-inflammatory property, continue to be recommended as the first-line treatment for patients with COP with symptomatic and progressive disease. Minimal data have been reported regarding alternative immunosuppressive agents in cases of CS-refractory COP. Some reports suggest that early treatment with CPM can be effective, particularly in patients who fail to respond to treatment with CS alone (12). The administration of CyA together with a CS in a fulminant patient with COP resulted in a successful outcome (13). In Case 1, because OP shadows and hypoxemia were severe and grew worse during hospitalization, the patient was successfully treated with PSL (40 mg/day) in combination with CyA.

Macrolides have not only antibacterial effects but also anti-inflammatory effects. Anti-inflammatory effects of macrolides in DPB were thought to reduce the influx of polymorphonuclear cells in the lung and decrease the production of cytokines involved in the inflammatory cascade, such as interleukin (IL)-8 and IL-1β (14). Apart from anti-inflammatory effects on polymorphonuclear cells or neutrophils, macrolides exhibit anti-inflammatory effects on T-cells by inhibiting cytokine gene expression (15).

As to macrolide treatment for COP, Ichikawa et al. reported a successful case using erythromycin (6). Stover et al. reported three cases of COP and three cases of radiation-related OP, which improved with CAM (7). Lee et al. successfully prescribed the macrolide roxithromycin (300 mg/day) in combination with CyA and CS for rapidly progressive COP (8). Oh et al. reported two cases of COP treated with CAM and only one responded to CAM (9).

According to a review of macrolide therapy in COP in which 29 patients were investigated, 20 patients initially received a macrolide as a single agent. Sixteen cases were cured with the medication after 3-14 months; however, the improvement took a longer time than that taken with glucocorticoids (GCs). It usually took 2-3 weeks for symptom improvement and 1 month for radiological improvement in chest images. Four patients had no improvement following macrolide treatment for 1 month and had to switch to GCs or a combination treatment with GCs. After that, the disease was well-controlled. The remaining nine patients were later treated with macrolides due to poor efficacy or side effects of GCs (16). It was speculated that the beneficial
effects of macrolides may be due to not only their immunosuppressive effect on polymorphonuclear cells and their products but also their influence on T-cells (9).

According to a case-based review, the PSL dosage for OP in patients with RA was 25-60 mg/day or 1-1.5 mg/kg/day (17). In Case 1, although CAM was ceased due to its adverse side effect of diarrhea, when OP shadows grew worse with PSL (5 mg/day) treatment, CAM was successfully added to the treatment. Case 2 was successfully treated with PSL (5 mg/day) in combination with CAM (400 mg/day). Case 3 was also successfully treated with PSL (10 mg/day) in combination with CAM (800 mg/day). Based on these findings, CAM treatment in OP associated with RA was thought to be effective as in COP and reduced a conventional dosage of PSL.

Elderly patients as those in Cases 1 and 2 tend to suffer from chronic diseases, such as diabetes mellitus, osteoporosis, infections and hypertension that are exacerbated by a CS, CAM treatment may therefore represent a useful option for elderly patients with OP associated with RA. Before CAM treatment can be adopted, patients who cannot accept a full dose of CS must be recruited and CAM treatment must be carried out after obtaining informed consent.

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