Successful Treatment of Infection-Triggered Acute Exacerbation of Idiopathic Pulmonary Fibrosis with Corticosteroids Combined with Macrolides

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ABSTRACT

Idiopathic pulmonary fibrosis (IPF) is a chronic progressive interstitial pneumonia (IP) with poor prognosis. Acute exacerbation (AE) of IPF (AE-IPF) has a substantial and sometimes fatal impact on prognosis. An effective pharmaceutical treatment for AE-IPF is lacking. Macrolides (MACs) have an anti-bacterial activity and anti-inflammatory effects, and IPF treatment with these agents has been recently reported. This report describes a case of infection-triggered AE-IPF treated with corticosteroids (CSs) combined with MACs. A 61-year-old male patient suffering from IPF previously treated with methyl-prednisolone (mPSL) (8 mg/day) was admitted because of fever, dry cough, and dyspnea. Reticular opacities (RO) on chest roentgenogram and ground-glass opacities (GGO) on high-resolution computed tomography (HRCT) exacerbated. The patient was diagnosed with influenza A and influenza A-triggered AE-IPF and was treated with permivir and mPSL (1 g/day) for 3 days. RO on chest roentgenogram further exacerbated, prompting the addition of erythromycin (EM), in consideration of its anti-inflammatory effects. Thereafter, the patient was successfully treated with mPSL or PSL combined with EM. During the clinical course, he experienced cytomegalovirus (CMV)-induced IP and/or CMV-triggered AE-IPF, being successfully treated with ganciclovir and mPSL or PSL combined with EM. Thereafter, the patient was treated with CSs combined with EM or clarithromycin. Approximately 3 months after initiating EM, RO on chest roentgenogram and GGO on HRCT considerably improved. This case shows that treatment with CSs combined with MACs may be effective in some cases of infection-triggered AE-IPF.

Key Words: Idiopathic pulmonary fibrosis, acute exacerbation, corticosteroids, macrolides

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a chronic progressive interstitial pneumonia (IP) with a poor prognosis. The median survival of IPF patients varies from 2 to 4 years after diagnosis. The natural history of IPF is heterogeneous, ranging from chronic stable symptoms to progressive respiratory failure, known as “acute exacerbation (AE).” AE is defined as an acute and severe respiratory deterioration associated with new bilateral lung infiltration on computed tomography (CT).

Most patients with IPF have a relatively slow clinical course, but up to 15% of patients experience an AE of IPF (AE-IPF) every year. A recent epidemiologic survey of Japanese patients with IPF showed that AE-IPF was the most common cause of death, despite treatment with drugs such as high-dose corticosteroids (CSs) (1).

Macrolides (MACs) such as erythromycin (EM), clarithromycin (CAM), and azithromycin (AZM) have an anti-bacterial activity and immunomodulatory effects, including anti-inflammatory effects. Successful MAC treatment for diffuse panbronchiolitis, cystic fibrosis, chronic obstructive pulmonary disease, and bronchial asthma has been reported.

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Recently, IPF treatment with MACs has been reported (1-4). Herein, a case of infection-triggered AE-IPF treated with CSs combined with MACs is described.

CASE REPORT

A 61-year-old male suffering from IPF previously treated with 8 mg/day of methyl-prednisolone (mPSL) for 3.5 years was admitted because of fever, dry cough, and acute progressive dyspnea within 1 week. Approximately 3 months before admission, fine crackles were audible in bilateral lower lung fields. White blood cell count (WBC), lactate dehydrogenase (LDH), C-reactive protein (CRP), and Krebs von den Lungen (KL)-6 levels, known to indicate the activity of IP (5, 6), were 10,280/µL, 222 U/L (normal range, <229 U/L), 0.20 mg/dL (normal range, <0.3 mg/dL), and 388 U/mL (normal range, <500 U/mL), respectively. Oxygen saturation by pulse oximetry (SpO2) was 96% in room air at rest. Chest roentgenogram (Figure 1A) and high-resolution computed tomography (HRCT) (Figure 2A) revealed reticular opacities (RO) and ground-glass opacities (GGO) accompanied by honeycombing, respectively. On admission, exacerbated fine crackles were audible in all lung fields. WBC, LDH, CRP, and KL-6 levels were 13,120/µL, 446 U/L, 9.18 mg/dL, and 1,007 U/mL, respectively. SpO2 decreased to 84% in room air at rest. β-D-glucan level was 3.0 pg/mL (normal range, <20 pg/mL), and a cytomegalovirus (CMV) pp65 antigenemia assay (LSI Medicine Corp., Tokyo, Japan) yielded negative results. A nasopharyngeal swab sample analyzed using a rapid test kit (BD Veritor System for Rapid Detection of Flu A+B Test, Japan Becton Dickinson Corp., Fukushima, Japan) indicated the presence of influenza A virus antigen. RO on chest roentgenogram (Figure 1B) and GGO on HRCT (Figure 2B) exacerbated. On the basis of these results, the patient was diagnosed with influenza A and influenza A-triggered AE-IPF. He was treated with peramivir (300 mg), an antiviral drug against influenza A virus, for 2 days and 1 g/day of mPSL for 3 days. Four days after initiating mPSL, dyspnea and SpO2 slightly improved, but RO on chest roentgenogram further exacerbated (Figure 1C). Considering the anti-inflammatory effects of MACs, intravenous EM (0.5 g three times a day for the long-term) was added to mPSL, the dosage of which was decreased from 1 g/day to 80 mg/day. The mPSL dosage was decreased at a rate of 10 mg/day for 5 days. After initiating EM, dyspnea and SpO2 gradually improved. Three weeks after initiating EM, WBC, LDH, CRP, and KL-6 levels were 6,700/µL, 330 U/L, 0.20 mg/dL, and 971 U/mL, respectively. RO on chest roentgenogram considerably improved with mPSL (50 mg/day) (Figure 1D). The patient was subsequently treated with PSL (50 mg/day) as an alternative to mPSL (50 mg/day). The PSL dosage was decreased at a rate of 5 mg/day for one week. Approximately 5 weeks after initiating EM, RO on chest roentgenogram again exacerbated on PSL (45 mg/day) (Figure 1E). WBC, LDH, and CRP were 2,580/µL, 429 U/L, and 7.75 mg/dL, respectively. Because a CMV pp65 antigenemia assay yielded positive results, the patient was diagnosed with CMV-induced IP and/or CMV-triggered AE-IPF. He was treated with 700 mg/day of ganciclovir (GCV), an antiviral drug against CMV. At this point, the patient received mPSL (80 mg/day) as an alternative to PSL (45 mg/day). The mPSL dosage was decreased at a rate of 10 mg/day for 5 days. Three weeks after initiating GCV, a CMV pp65 antigenemia assay yielded negative results, and RO on chest roentgenogram moderately improved with mPSL (50 mg/day) treatment. The patient was treated with CAM (800 mg/day) for 2 weeks. Overall, during the clinical course, the patient received MACs for a total of 2.5 months. Approximately 3 months after initiating EM, WBC, LDH, CRP, and KL-6 levels were 8,650/µL, 277 U/L, 1.08 mg/dL, and 476 U/mL, respectively. SpO2 increased to 95% in room air at rest. GGO on HRCT (Figure 2C) and RO on chest roentgenogram (Figure 1F) considerably improved with PSL (25 mg/day).
Four days after initiating methyl-prednisolone, chest roentgenogram revealed further RO exacerbation.

Three weeks after initiating erythromycin (EM), chest roentgenogram revealed considerable RO improvement.

Approximately 5 weeks after initiating EM, chest roentgenogram revealed RO exacerbation.

Approximately 3 months after initiating EM, chest roentgenogram revealed considerable RO improvement.
Figure 2. High-resolution computed tomography chest images.
Figure 2A. Approximately 3 months before admission, high-resolution computed tomography (HRCT) revealed ground-glass opacities (GGO) accompanied by honeycombing.

Figure 2B. On admission, HRCT revealed exacerbated GGO.

DISCUSSION

AE-IPF has a substantial impact on patients’ prognosis. The reported median survival after AE ranges between 22 days and 4.2 months, with a hospital mortality rate of 27%–96% (7). An effective pharmaceutical treatment for AE-IPF is lacking. Although there is insufficient evidence for drug treatment, high-dose steroid therapy, cyclosporine A, and warfarin are priority recommendations. Although not listed in recommendations, immunosuppressants such as cyclophosphamide or tacrolimus and polymyxin B immobilized fiber column hemoperfusion have been reported to be helpful (7). Tomioka et al. described a case of AE-IPF which improved with the use of nintedanib alone (8). In the present case, mPSL pulse therapy was considered insufficiently effective, and intravenous EM was added because of its anti-inflammatory effects. Thereafter, the patient was successfully treated with mPSL or PSL combined with EM. However, RO on chest roentgenogram again exacerbated, which was believed to be caused by CMV-induced IP and/or CMV-triggered AE-IPF. The patient was successfully treated with GCV and CSs combined with EM. Thereafter, the patient was treated with CSs combined with MACs, having received MACs for a total of 2.5 months. Approximately 3 months after initiating EM, RO on chest roentgenogram and GGO on HRCT considerably improved, resulting in further improved laboratory data, including KL-6. In view of these results, treatment with CSs combined with MACs was considered effective for infection-triggered AE-IPF.

As previously mentioned, MACs have an anti-bacterial activity and immunomodulatory – including anti-inflammatory – effects. MACs use in the treatment of IPF has been reported (1-4). Jouneau et al. (2) described a case of airway-centered interstitial fibrosis, a distinct type of lung interstitial fibrosis, treated with CAM. This patient was initially treated with PSL but with no efficacy outcomes and pulmonary function test worsening, prompting the addition of CAM (500 mg/day for 1 month and then 250 mg/day onward) to PSL. Results showed a stop in lung function decline and no change in chest CT. We have also previously reported a case of IPF that gradually exacerbated over 2 months, which was treated with CAM (800 mg/day) alone for the long-term (3). A considerable GGO improvement on chest HRCT was observed in this patient. Kuse et al. (4) reported that long-term MAC combined with conventional therapy could reduce the incidence of AE and showed a significant IPF overall survival improvement. Regarding AE-IPF treatment, Kawamura et al. (1) showed that AZM (500 mg/day) treatment for 5 days improved survival in a patient with idiopathic AE-IPF. In the present case, considering the efficacy of AZM treatment for 5 days, administration of MACs for 2.5 months could have been obviated in this patient.

Cai et al. (9) reported that alveolar macrophages from bronchiolitis obliterans organizing pneumonia (OP) patients produce abundant proinflammatory cytokines, which may be pivotal in disease pathogenesis. Furthermore, they found that CAM and AZM inhibit the alveolar macrophage production of these cytokines in a dose-dependent way. Surgical lung biopsy of AE-IPF revealed diffuse alveolar damage (DAD), honeycomb changes, and OP (10). On the basis of these results, a direct effect of MACs on OP areas or DAD by reduction of alveolar macrophage priming can be admitted (2). Because AE-IPF outcomes are very poor, MAC treatment may have potentially beneficial effects on AE-IPF.
No conflict of interest was declared by the authors.

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