Deterioration of the Immune Response Induced by Sulfamethoxazole-trimethoprim in a Rheumatoid Arthritis Patient with *Pneumocystis jirovecii* Pneumonia

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Abstract

A 73-year-old woman with rheumatoid arthritis treated with methotrexate and prednisolone was admitted with dyspnea and ground-glass opacity on chest CT. We diagnosed her with *Pneumocystis jirovecii* pneumonia (PCP) based on a positive PCR analysis of *Pneumocystis jirovecii* and the presence of cysts in bronchoalveolar lavage fluid. The PaO₂ was 74.7 Torr on room air, and treatment with sulfamethoxazole-trimethoprim only was initiated. The hypoxemia and ground-glass opacity increased on hospital day 3, and the administration of adjunctive steroid therapy resulted in an improvement in the patient's condition. Although patients with PCP with HIV infection and hypoxemia are often treated with adjunctive steroid therapy to prevent adverse immune reactions, the efficacy of additive steroid administration in case of non-HIV PCP has not been established.

Key words: adjunctive corticosteroids therapy, *Pneumocystis jirovecii* pneumonia, rheumatoid arthritis, sulfamethoxazole-trimethoprim

(Intern Med 53: 1137-1141, 2014)

(DOI: 10.2169/internalmedicine.53.1505)

Introduction

Patients with rheumatoid arthritis (RA) are usually treated with immunosuppressive agents, such as methotrexate (MTX) and biological drugs, which inhibit the progression of articular destruction. However, such treatment can also result in various infections.

The first case report of *Pneumocystis jirovecii* pneumonia (PCP) in a patient with RA treated with an immunosuppressive agent was published in 1983 (1). Since then, there have been many reports of PCP in patients with RA. PCP is often associated with HIV, and guidelines for the treatment of PCP in HIV patients have been published (2). According to these guidelines, sulfamethoxazole-trimethoprim (SMX-TMP) is widely used. Adjunctive corticosteroid therapy is also recommended in case of PCP in HIV patients with a PaO₂ of <70 Torr or alveolar-arterial oxygen gradient

(AaDO₂) of ≥35 Torr. In practice, PCP is treated with SMX-TMP in RA patients according to the treatment regimen for PCP associated with HIV. However, the use of adjunctive corticosteroid treatment for PCP in patients with RA has not yet been established (3, 4). We experienced a case of PCP in a RA patient receiving treatment with MTX and steroid therapy. We administered SMX-TMP alone; however, the patient developed hypoxemia and the imaging findings worsened. The administration of adjunctive corticosteroid therapy improved the patient's condition. The present case and a review of cases of PCP at our hospital provide useful information for physicians.

Case Report

A 73-year-old woman who had been suffering from bronchiectasis for 13 years presented to our hospital complaining of a fever and cough lasting for three days. She had been

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Received for publication August 6, 2013; Accepted for publication December 5, 2013

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Figure 1. A chest X-ray obtained on admission showed a tram line sign in the left middle lung field and ground-glass opacity in both lower lung fields.

diagnosed with RA two years before presentation and was initially treated with MTX. Because the control of the RA was incomplete, the dose of MTX was gradually increased to 10 mg weekly, and prednisolone (1 mg/day) was added. She was diagnosed with class 1, stage I RA upon presentation to our hospital.

On admission, the patient's body temperature was 38.4°C and her respiratory rate was 18 breaths/min. Chest auscultation revealed bilateral fine crackles. An arterial blood gas analysis on room air showed a pH of 7.44, PaO₂ of 74.7 Torr, PaCO₂ of 37.2 Torr, and HCO₃⁻ of 25.0 mmol/L. The laboratory findings were as follows: white blood cell count 6,100/μL (neutrophils: 60.6%, lymphocytes: 23.6%, macrophages: 6.1%, eosinophils: 9.4%, basophils: 0.3%), CD4-positive T cells 797/μL, lactose dehydrogenase 230 IU/L, C-reactive protein 6.1 mg/dL, KL-6 613 U/mL, SP-D 183.7 ng/mL, MMP-3 177.5 ng/mL and β-D-glucan 17.3 pg/mL (FungiTec G Test MK; Seikagaku Kogyo Corp., Tokyo, Japan). A chest X-ray (Fig. 1) showed ground-glass opacity (GGO) in the middle and lower lung fields. High-resolution computed tomography (HRCT) (Fig. 2a) showed GGO with thickened interlobular septa.

We suspected the patient with PCP; however drug-induced lung disease (by MTX) and cytomegalovirus pneumonia were included in the differential diagnosis. We then stopped the MTX therapy and initiated the administration of SMX-TMP at a dose of TMP of 480 mg daily. Ganciclovir was not administered because the cytomegalovirus antigenemia assay was negative. Tazobactam/piperacillin and clarithromycin were also added to cover bacterial infection. Bronchoscopy was performed on the second hospital day. Bronchoalveolar lavage performed in the right middle lobe recovered 95 mL of 150 mL (63%) with 10.3×10⁵/mL cells (neutrophils: 4.2%, lymphocytes: 73.6%, eosinophils: 4.3% and macrophages: 17.9%), and the CD4/CD8 ratio was 8.3. No significant pathogens were cultured from the bronchoalveolar lavage fluid. The results of polymerase chain reaction

(PCR) for *P. jirovecii* were positive, and para-aminosalicylic acid and Grocott-Gomori methenamine silver nitrate staining of the bronchoalveolar lavage fluid revealed cysts of *P. jirovecii* (Fig. 3). The patient was then diagnosed with PCP, and SMX-TMP was administered for 14 days followed by treatment with 80 mg daily as preventive therapy for PCP. On the third hospital day, she developed dyspnea and her coughing increased. In addition, the PaO₂ on room air decreased to 53.7 Torr. A chest X-ray and HRCT performed on the fourth hospital day showed an increase in GGO (Fig. 2b). We considered these findings to reflect an immune response due to the use of treatment for PCP with SMX-TMP alone. Therefore, we administered methylprednisolone (1,000 mg/day intravenously for three days). The patient's respiratory condition improved, and the SpO₂ recovered to 95% on room air by the sixth hospital day. The dose of prednisolone was then tapered to 30 mg/day orally for three days followed by 20 mg/day for five days. The radiological findings also improved, and she was discharged on the 25th hospital day. The β-D-glucan level was not elevated at any time during the patient's hospital course (Fig. 4). It is known that the level of KL-6, a marker of interstitial lung disease, is increased in patients with PCP (5). The KL-6 level in our patient was 1,129 U/mL on the 16th hospital day and 1,337 U/mL on the 24th hospital day. The dose of prednisolone was tapered to 6 mg and salazosulfapyridine was added to the medication regimen. Prophylactic SMX-TMP was also introduced. The patient continues to be followed on an outpatient basis without recurrence of PCP.

Discussion

In the present case, PCP occurred in a patient who was being treated with MTX and prednisolone for RA. The patient exhibited respiratory symptoms with GGO in a large area of her lungs. We suspected a diagnosis of PCP with drug-induced (MTX) lung disease and cytomegalovirus pneumonia as the differential diagnoses. The β-D-glucan level was not elevated throughout the patient's clinical course; however, a PCR analysis of the bronchoalveolar lavage fluid was positive for *P. jirovecii*, and Grocott-Gomori methenamine silver nitrate staining of the lavage fluid showed cysts of *P. jirovecii*. Therefore, we diagnosed the patient with PCP.

The diagnosis of PCP is established in immunosuppressed patients with typical imaging and pathological findings (2). The β-D-glucan level is also a practical parameter for determining a diagnosis of PCP. It has been reported that a cutoff value for the β-D-glucan level of 31.1 pg/mL (WAKO method) exhibits a sensitivity of 92.3% and a specificity of 86.1% (6). Although the β-D-glucan levels in our patient was not elevated at any time during the course of PCP, it was difficult to distinguish PCP from MTX-induced pneumonitis. Samples obtained via bronchoscopy yielded diagnostic results, thus suggesting the usefulness of bronchoscopic examinations in patients with PCP. A diagnosis of

Figure 2. Chest computed tomography performed on admission (a) and the third hospital day (b) showed worsening of the bilateral ground-glass opacity.

Figure 3. Cytological findings of the bronchoalveolar lavage fluid. (a) Para-aminosalicylic acid and (b) Grocott-Gomori methenamine silver nitrate staining of the bronchoalveolar lavage fluid revealed cysts of *Pneumocystis jirovecii*.

PCP should never be ruled out simply because the β -D-glucan level is not increased, and bronchoscopic examinations should be performed if PCP is suspected.

PCP is generally treated with SMX-TMP. However, the respiratory condition and radiologic findings of PCP patients with HIV treated with SMX-TMP alone can sometimes deteriorate. The cause of lung injury is not believed to be due to the *P. jirovecii* pathogen itself, but rather to the immune response to treatment (7, 8). Therefore, in HIV patients with PCP and a PaO_2 value of <70 Torr or AaDO_2 value of ≥ 35 Torr, the administration of adjunctive corticosteroid therapy is recommended within 72 hours of the start of SMX-TMP

therapy (9). However, it is not clear whether adjunctive corticosteroids should be administered in non-HIV patients with PCP (10). Previous studies of small populations have reported that the use of adjunctive corticosteroid treatment in non-HIV patients with PCP and hypoxia shortens the duration of both mechanical ventilation and hospitalization (3, 4).

In our hospital, 23 PCP patients with RA were hospitalized between September 2001 and November 2012 (11). Among these patients, six had a PaO_2 of ≥ 70 Torr, all six of whom had also received SMX-TMP only as the initial treatment. Subsequently, the radiological and respiratory conditions of two of these patients (including the present patient) worsened, requiring the administration of adjunctive corticosteroids (Table). The respiratory conditions of both patients deteriorated on the third and second days, respectively, after starting SMX-TMP, similar to the course of PCP observed in HIV patients. The present patient did not require oxygen upon admission for PCP, although oxygen therapy was required on the third day after the initiation of the SMX-TMP treatment. The other patient required oxygen at a dose of 5 L/min on the second day after the initiation of SMX-TMP therapy. The respiratory conditions of these two patients improved with adjunctive corticosteroid therapy; therefore, the administration of oxygen was discontinued on the 15th and 21st days, respectively, after the start of adjunctive corticosteroid therapy. The remaining 17 patients, with a PaO_2 value of <70 Torr or AaDO_2 value of ≥ 35 Torr, were treated with both SMX-TMP and adjunctive corticosteroid therapy.

We experienced a patient with RA whose respiratory condition and radiological findings worsened following the administration of SMX-TMP alone for the treatment of PCP. The patient's PaO_2 was ≥ 70 Torr. This case shows that PCP may deteriorate to severe hypoxemia in RA patients without hypoxia after initiating SMX-TMP therapy. In such cases, the use of adjunctive corticosteroid therapy may be effective for improving the patient's respiratory impairment. Careful attention should be paid to starting adjunctive corticosteroid therapy when the patient's respiratory condition deteriorates during treatment of PCP with SMX-TMP alone. Further inves-

Figure 4. Clinical course. We suspected the patient of having *Pneumocystis* pneumonia, and sulfamethoxazole-trimethoprim (SMX/TMP) was administered at a dose of TMP of 480 mg daily for 14 days followed by treatment with 80 mg daily as preventive therapy for PCP. On the third hospital day, the SpO₂ on room air decreased to 91%. A chest X-ray performed on the fourth hospital day showed an increase in ground-glass opacity. Therefore, we administered methylprednisolone (mPSL) at a dose of 1,000 mg/day intravenously for three days. The patient's respiratory condition improved, and the SpO₂ recovered to 95% on room air by the sixth hospital day. The dose of oral prednisolone (PSL) was then tapered to 30 mg/day for three days followed by 20 mg/day for five days. The radiological findings also improved, and the patient was discharged on the 25th hospital day. The β-D-glucan level was not elevated throughout the treatment course. SpO₂: arterial oxygen saturation measured on pulse oximetry, AaDO₂: alveolar-arterial oxygen gradient.

Table. Characteristics of *Pneumocystis* Pneumonia Patients with RA Treated at Our Hospital

	Sex	Age	β-D-glucan	PaO ₂	Treatment of PCP	Treatment of RA	Outcome
Case 1	F	72	20.0	75.1	SMX/TMP only	MTX + Infliximab	Alive
Case 2	F	68	49.6	79.5	SMX/TMP only	MTX + PSL	Alive
Case 3	M	68	45.0	83.0	SMX/TMP → Day2~PSL 60mg daily	PSL + Bucillamine	Alive
Case 4	F	48	84.6	85.8	SMX/TMP only	GST	Alive
Case 5	F	75	161.8	90.7	SMX/TMP only	MTX	Alive
This case	F	73	17.3	74.7	SMX/TMP → Day4~mPSL 1g daily	MTX + PSL	Alive

RA: rheumatoid arthritis, F: female, M: male, PCP: *Pneumocystis jirovecii* pneumonia, SMX/TMP: sulfamethoxazole-trimethoprim, PSL: prednisolone, MTX: methotrexate, GST: gold sodium thiomalate

tigation is necessary to determine whether corticosteroid therapy should be routinely added to the SMX-TMP treatment regimen in PCP patients with RA with a PaO₂ of ≥70 Torr.

The authors state that they have no Conflict of Interest (COI).

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