Mod Rheumatol (2006) 16:36–38
DOI 10.1007/s10165-005-0443-5
© Japan College of Rheumatology 2006

CASE REPORT

Yuko Kaneko · Akira Suwa · Yasuo Ikeda
Michito Hirakata

Pneumocystis jiroveci pneumonia associated with low-dose methotrexate treatment for rheumatoid arthritis: report of two cases and review of the literature

Received: September 1, 2005 / Accepted: October 19, 2005

Abstract Low-dose methotrexate (MTX) therapy is widely used for rheumatoid arthritis (RA) because of its favorable efficacy and toxicity profile. Although *Pneumocystis jiroveci* pneumonia (PCP) is most often seen in severely immunosuppressed patients, PCP complicating low-dose MTX therapy for RA has been reported to sometimes occur. We herein report two cases of patients who developed PCP during treatment with low-dose MTX, and discuss the importance of prophylaxis for this opportunistic infection.

Key words Methotrexate (MTX) · *Pneumocystis jiroveci* pneumonia (PCP) · Prophylaxis · Rheumatoid arthritis (RA)

Introduction

Low-dose weekly pulse methotrexate (MTX) therapy is most commonly used for rheumatoid arthritis (RA) because of its favorable efficacy to reduce symptoms and prevent progressive structural damage.[1] However, this therapy has been recently implicated as a risk factor for opportunistic infections. *Pneumocystis jiroveci* pneumonia (PCP) is most often seen in severely immunosuppressed patients related to acquired immunodeficiency syndrome (AIDS) and treatment with strong cytotoxic agents or immunosuppressive drugs. In 1983 PCP complicating low-dose MTX therapy for RA was reported.[2] Due to the wide diversity for the options for the treatment of RA including biological agents, we should take greater care of PCP. We herein describe two patients who developed PCP during low-dose MTX therapy and discuss the importance of appropriate prophylaxis.

Y. Kaneko (✉) · A. Suwa · Y. Ikeda · M. Hirakata
Department of Internal Medicine, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan
Tel. +81-3-3353-1211 (ext. 62315); Fax +81-3-5379-5037
e-mail: ykaneko@sc.itc.keio.ac.jp

Case reports

Patient 1

A 68-year-old woman suffering from seropositive RA for 17 years had been treated with MTX in a dosage of 5 mg/week, prednisolone (PSL) 6 mg/day, bucillamine 200 mg/day, and diclofenac 25 mg/day. After 147 months of MTX therapy, she began to complain of fever and dyspnea. On admission her body temperature was 40°C and a lung examination showed bilateral crackles. Laboratory examinations showed: white blood cells (WBC) 13 200/μl (lymphocytes 660/μl), hemoglobin 14.1 g/dl, platelets 20.7×10^4/μl, lactate dehydrogenase (LDH) 480 IU/l, C-reactive protein (CRP) 11 mg/dl, IgG 938 mg/dl, β-D-glucan >600 pg/ml, KL-6 749 U/l. Her arterial blood gas analysis (BGA) showed type I respiratory failure (PaO_2 52 torr, $PaCO_2$ 27 torr, pH 7.57). A chest radiograph revealed bilateral ground-glass infiltrates and reticular shadows (Fig. 1). A polymerase chain reaction (PCR) assay of bronchoalveolar lavage (BAL) fluid showed *Pneumocystis* (PC). Aerobe, anaerobe, and fungal cultures of lavage fluid and cytomegalovirus (CMV) antigenemia were negative. Methotrexate was immediately discontinued, and high-dose trimethopurim sulfamethoxazole (TMP-SMX) and methylprednisolone (mPSL) pulse therapy was administered, resulting in both a clinical and radiographic improvement.

Patient 2

A 73-year-old woman suffering from malignant RA for 14 years had been treated with MTX in a dosage of 7.5 mg/week, PSL 16 mg/day, and diclofenac 75 mg/day. After 13 months of MTX therapy, she developed general malaise and gait disturbance. On admission she was afebrile and coarse crackles were audible in the left lung field. Laboratory examinations showed: WBC 4400/μl (lymphocytes 44/μl), hemoglobin 10.4 g/dl, platelets 20.7×10^4/μl, LDH 512 U/l, CRP 23 mg/dl, IgG 477 mg/dl, β-D-glucan 424 pg/ml. Arterial BGA revealed PaO_2 25 torr, $PaCO_2$ 42 torr, and pH

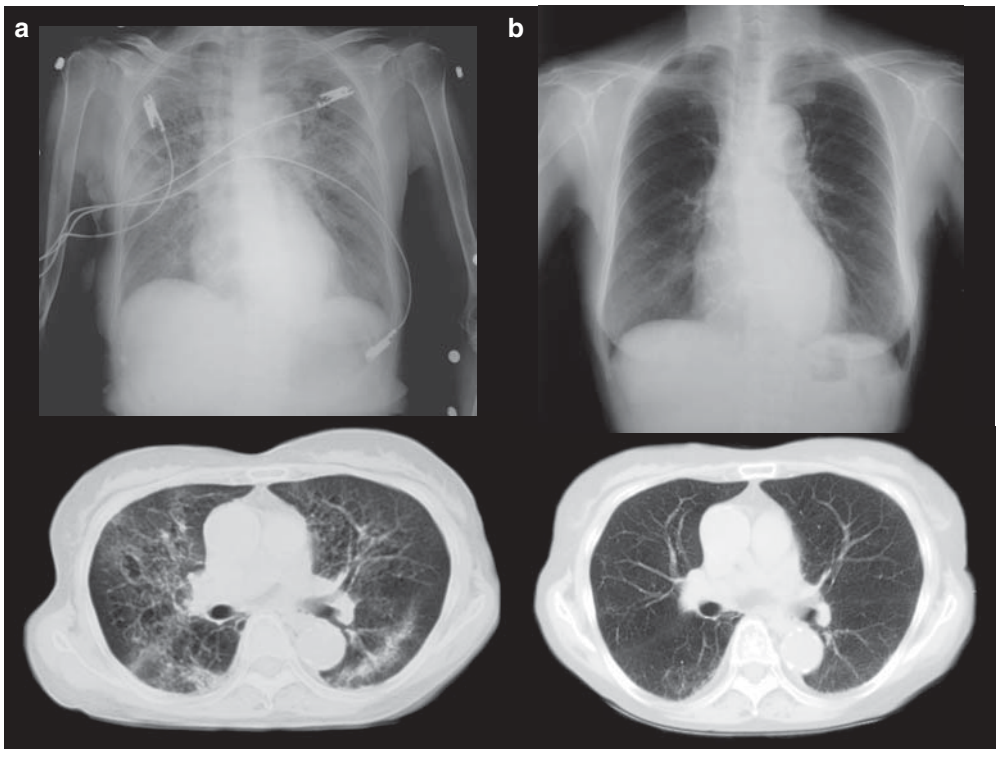

Fig. 1a,b. Chest X-ray and computed tomography. **a** Chest radiographs revealed bilateral ground-glass infiltrates and reticular shadows. **b** The shadows disappeared after treatment with prednisolone and trimethopurim/sulfamethoxazole

7.51, and ventilation support was required. A chest radiograph revealed interstitial and alveolar infiltrations, preferentially in the left lung. Bronchoalveolar lavage fluid revealed PC by Grocotto staining. High-dose intravenous TMP-SMX was given for 7 days together with mPSL pulse therapy. TMP-SMX was changed to pentamidine isetionate, since her symptoms were complicated by severe pancytopenia due to TMP-SMX. However, she died of *Aspergillus pneumonia* and disseminated intravenous coagulation 3 weeks later. Autopsy revealed infarctions of multiple organs with intravenous thrombi in addition to diffuse fibrosis in her bilateral lungs.

Discussion

We herein reported two patients who developed PCP during low-dose MTX therapy. A good response was achieved by early diagnosis and combination therapy with TMP-SMX and mPSL in patient 1, while patient 2 was unfortunately complicated with total *Aspergillus* infection caused by a severely immunocompromised state due to concomitant PSL use, hypogammaglobulinemia, and pancytopenia. The prognosis of PCP improved with advanced treatment, but PCP often remains fatal even today.

Since the first report in 1983,[2] the occurrence of PCP during treatment with low-dose MTX in RA has attracted a great deal of attention. Formerly the PC organism was thought to be a protozoan named *Pneumocystis carinii*, but the organism was later revealed to be a fungus and not related to zoonosis by DNA analysis. As a result, it is now referred to as *Pneumocystis jiroveci*, which causes pneumonia in humans.[3] *Pneumocystis jiroveci* pneumonia is most often seen in severely immunosuppressed patients, related to AIDS and treatment with strongly cytotoxic agents or immunosuppressive drugs. The use of a PSL dose of greater than 30 mg/day was reported to be associated with a risk of developing PCP.[4] Recently, PCP complicating low-dose MTX therapy for RA has been reported to sometimes occur and it thus should be considered in the differential diagnosis for interstitial pneumonitis, including MTX-induced pneumonitis. *Pneumocystis jiroveci* pneumonia is definitely diagnosed by the detection of PC organisms in appropriate respiratory specimens using Grocotto methanamine silver staining and an immunofluorescence assay. The PCR technique has been reported to be useful for an early diagnosis. However, the asymptomatic carriage of PC has also been reported in 44% in the patients who receive corticosteroids equivalent to >20 mg/day PSL.[5] The polymerase chain reaction is superior in sensitivity to staining, but inferior in specificity.[6] Clinical findings, laboratory data, and response to treatment should be considered when confirming the diagnosis. Because the BAL fluid of patient 1 was negative in Grocotto staining but positive in PCR, we diagnosed her as having PCP by taking all factors into consideration after we started to administer PSL and TMP-SMX.

The pulmonary adverse effects associated with MTX are reported to occur in 1%–5% of cases,[7,8] and opportunistic infections, such as PCP, CMV pneumonia, disseminated herpes zoster, cryptococcosis, and widespread nocardiosis[9–11] have been found to accumulate with the increased use of MTX. Although the mechanisms by which

MTX is effective for RA are still unclear, many anti-inflammatory and immunosuppressive actions, such as the inhibition of cellular proliferation, alterations in the lymphocyte subsets, a decreased cytokine production, the suppression of T-cell activation, and cell adhesion molecules,[1–12] have all been hypothesized to play a role. The concomitant use of nonsteroidal anti-inflammatory drugs, which can raise the plasma concentration of MTX by displacing it from albumin binding sites and impairing its renal excretion, could also have potentiated the MTX toxicity.[13] Furthermore, the combination therapy of MTX and corticosteroid and/or other immunosuppressants has been suggested to be a risk factor for opportunistic infections. Prednisolone had been used in our two cases. It was interesting to note that patient 1 developed PCP while taking low-dose PSL. Lymphocytopenia may contribute to susceptibility for PCP, but PCP sometimes occurs in patients with a normal lymphocyte count.[14] In patient 1, the lymphocytes decreased at the onset of PCP, but they had been 1000–1200/μl for 3 months before the occurrence of PCP. In patient 2 the lymphocytes had been 250–300/μl for 3 months before PCP. Therefore the lymphocyte count is not considered to always be a risk factor for PCP.

Inokuma et al. reported the prevalence of PCP associated with autoimmune disease in 13 hospitals, which turned out to be 69 of 10 290 admitted patients between 1997 and 2001. Among them, 6 of 10 patients with RA were treated with MTX. It is noteworthy that all three patients who were treated with less than 10 mg/day PSL were receiving concomitant MTX, suggesting the administration of MTX to be a strong risk factor for developing PCP in RA.[15]

The clinical significance of prophylaxis for PCP remains controversial. However, because there has been a wide diversity in the treatment for RA including biological agents that are capable of inducing an immunocompromised state, we should take greater care with PCP. One case was previously reported to develop PCP after infliximab was used.[16] In 2005, the Japanese Ministry of Health, Labor and Welfare Study Group published a guideline in which PCP prophylaxis was recommended when patients of over 50 years old received either corticosteroids equivalent to >1.2 mg/kg per day PSL or corticosteroids equivalent to >0.8 mg/kg per day PSL and concomitant immunosuppressive agents, or in patients whose lymphocyte count was less than 500/μl.[15] The recommended dosage is TMP-SMX 4–8 g/week or aerosolized pentamidine isetionate 300 mg/2–4 weeks as a prophylaxis for PCP with autoimmune disease.[15] In patients infected with human immunodeficiency virus, Atovaquone or Azithromycin can also be used. Because TMP-SMX has a synergistic effect with MTX in inactivating dihydrofolate reductase and has an effect in increasing free MTX, the combination of TMP-SMX and MTX has a great risk of inducing pancytopenia.[17,18] We should therefore consider reducing the MTX dose when also using TMP-SMX or choosing other drugs, such as Azithromycin, as a prophylaxis for PCP.

In conclusion, PCP is a fatal complication that may occur in patients receiving low-dose MTX therapy for RA, and the optimal prophylaxis for PCP should be selected based on the patient's age, the severity of lymphocytopenia, or according to the concomitant use of corticosteroids and/or other immunosuppressive agents.

References

1. Cronstein BN. Low-dose methotrexate: a mainstay in the treatment of rheumatoid arthritis. Pharmacol Rev 2005;57:163–72.
2. Perruquet JL, Harrington TM, Davis DE. *Pneumocystis carinii* pneumonia following methotrexate therapy for rheumatoid arthritis. Arthritis Rheum 1983;26:1291–2.
3. Stringer JR, Beard CB, Miller RF, Wakefield AE. A new name (*Pneumocystis jiroveci*) for pneumocystis from humans. Emerg Infect Dis 2002;8:891–6.
4. Roblot F, Godet C, Le Moal G, Garo B, Faouzi Souala M, Dary M, et al. Analysis of underlying diseases and prognosis factors associated with *Pneumocystis carinii* pneumonia in immunocompromised HIV-negative patients. Eur J Clin Microbiol Infect Dis 2002;21:523–31.
5. Maskell NA, Waine DJ, Lindley A, Pepperall JCT, Wakefield AE, Miller RF, et al. Asymptomatic carriage of *Pneumocyctis jiroveci* in subjects undergoing bronchoscopy: a prospective study. Thorax 2003;58:594–7.
6. Flori P, Bellete B, Durand F, Raberin H, Cazorla C, Hafid J, et al. Comparison between real-time PCR, conventional PCR and different staining techniques for diagnosing *Pneumocystis jiroveci* pneumonia from bronchoalveolar lavage specimens. J Med Microbiol 2004;53:603–7.
7. Barrera P, Laan RF, van RPL, Dekhuijzen PN, Boerbooms AM, van de Putte LB. Methotrexate-related pulmonary complications in rheumatoid arthritis. Ann Rheum Dis 1994;53:434–9.
8. Hilliquin P, Renoux M, Perrot S, Puechal X, Menkes CJ. Occurrence of pulmonary complications during methotrexate therapy in rheumatoid arthritis. Br J Rheumatol 1996;35:441–5.
9. Clerc D, Brousse C, Mariette X, Bennet P, Bisson M. Cytomegalovirus pneumonia in a patient with rheumatoid arthritis treated with low dose methotrexate and prednisone. Ann Rheum Dis 1991;50:67.
10. Shiroky JB, Frost A, Skelton JD, Haegert DG, Newkirk MM, Neville C. Complications of immunosuppression associated with weekly low dose methotrexate. J Rheumatol 1991;18:1172–5.
11. LeMense GP, Sahn SA. Opportunistic infection during treatment with low dose methotrexate. Am J Respir Crit Care Med 1994; 150:258–60.
12. Johnston A, Gudjonsson JE, Sigmundsdottir H, Ludviksson BR, Valdimarsson H. The anti-inflammatory action on methotrexate is not mediated by lymphocyte apoptosis, but by the suppression of activation and adhesion molecules. Clin Immunol 2004;114:154–63.
13. Stenger AA, Houtman PM, Bruyn GA, Eggink HF, Pasma HR. Pneumocystis carinii pneumonia associated with low dose methotrexate treatment for rheumatoid arthritis. Scand J Rheumatol 1994;23:51–3.
14. Takeda Y, Tsuji T, Misumi M, Ideguchi H, Ueda A, Ohno S, et al. Pneumocystis carinii pneumonia associated with low dose methotrexate treatment for malignant rheumatoid arthritis. Rinsho Riumachi 2001;13:293–9.
15. Hashimoto H. Prophylaxis of *Pneumocystis jiroveci* pneumonia in autoimmune disease (in Japanese). In: Hashimoto H, editor. Clinical guideline. Tokyo: Japanese Ministry of Health, Labour and Welfare Study Group on complication and treatment of immune disease; 2005. p. 14–9.
16. Tai TL, O'Rourke KP, McWeeney M, Burke CM, Sheehan K, Barry M. Pneumocystis carinii pneumonia following a second infusion of infliximab. Rheumatology 2002;41:951–2.
17. Ferrazzini G, Klein J, Sulh H, Chung D, Griesbrecht E, Koren G. Interaction between trimethoprim-sulfamethoxazole and methotrexate in children with leukemia. J Pediatr 1990;117:823–6.
18. Groenendal H, Rampen FH. Methotrexate and trimethoprim-sulphamethoxazole – a potentially hazardous combination. Clin Exp Dermatol 1990;15:358–60.