A Cluster of *Pneumocystis jirovecii* Infection Among Outpatients with Rheumatoid Arthritis

To the Editor:

Pneumocystis jirovecii is the causative agent of Pneumocystis pneumonia (PCP), well known to be one of the most frequent and serious complications occurring under immunocompromised conditions such as HIV infection. Accumulating reports have also shown the clinical significance of PCP in patients with malignancy, in transplant recipients, and in patients receiving immunosuppressive therapy. Indeed, a recent postmarketing surveillance report by the Japan College of Rheumatology indicated a high incidence of PCP in patients with rheumatoid arthritis (RA) receiving the anti-tumor necrosis factor-α agents infliximab and etanercept (0.4% and 0.2%, respectively). Despite recent advances in understanding human Pneumocystis infection, the exact mode of its transmission and acquisition remains unclear, and both the source and reservoir for infection in humans have not yet been established[1]. We describe a cluster of asymptomatic carriage of *P. jirovecii* and/or PCP occurring among outpatients with RA. Clinical and epidemiological data strongly suggest person-to-person transmission of *P. jirovecii* in our outpatient facility as the predominant route of acquisition.

Kumamoto Saishunsou National Hospital is a 500-bed general hospital consisting of 3 buildings, located in the suburbs of Kumamoto City in western Japan. One building accommodates an outpatient clinic and a radiodiagnostic facility, which are both shared by all outpatients; about 200 outpatients from 12 clinical sections visit this building daily. Accordingly, patients with RA visit this building for regular checkups and treatment. Since March 2005, we have advised RA patients to undergo molecular testing by polymerase chain reaction (PCR) for *P. jirovecii* on induced sputum, since it has been noted that these persons are at increased risk of *P. jirovecii* infection[2,3]. The use of prophylactic agents against this organism is recommended for all carriers when not contraindicated. Detailed protocols were described in our previous study[2]. To date, we have performed PCR tests on 132 outpatients with RA. As shown in Figure 1, during the first 2 years after institution of PCR testing, only one case of PCP was observed in our RA patient group (case 1) and no asymptomatic carriers were found. Between November 2006 and October 2008, we found 9 cases of asymptomatic carriage of this organism (cases 3–5, 7, 9–11, 13, and 14), and among these, 3 patients (cases 9, 13, and 14) developed PCP within 1 month. The other 6 tested negative for *P. jirovecii* DNA after 2–4 weeks of primary prophylaxis. During this period, we encountered 5 additional cases of PCP in RA outpatients who had not yet undergone PCR testing (cases 2, 6, 8, 12, and 15). Patients' respiratory symptoms were nonspecific and nonsevere, and their high resolution computerized tomography scans revealed diffuse ground-glass opacities. Within 2 weeks of hospitalization and treatment, all the PCP cases tested negative for *P. jirovecii* DNA. All patients with asymptomatic carriage and/or PCP development had received low doses (6–10 mg/week) of methotrexate (MTX), and their peripheral lymphocyte counts were maintained at levels above 500/μl. They had not received high doses of prednisolone, and no patient was known to be HIV-positive. Since *P. jirovecii* was eradicated in these patients, they have continued to maintain negative PCR results without prophylactic intervention, even after resuming immunosuppressive therapy for RA. In addition, we have found no new *P. jirovecii*-positive cases in the year since the last PCP case was cured in October 2008.

In recent reports on cluster outbreaks of PCP cases among immuno-

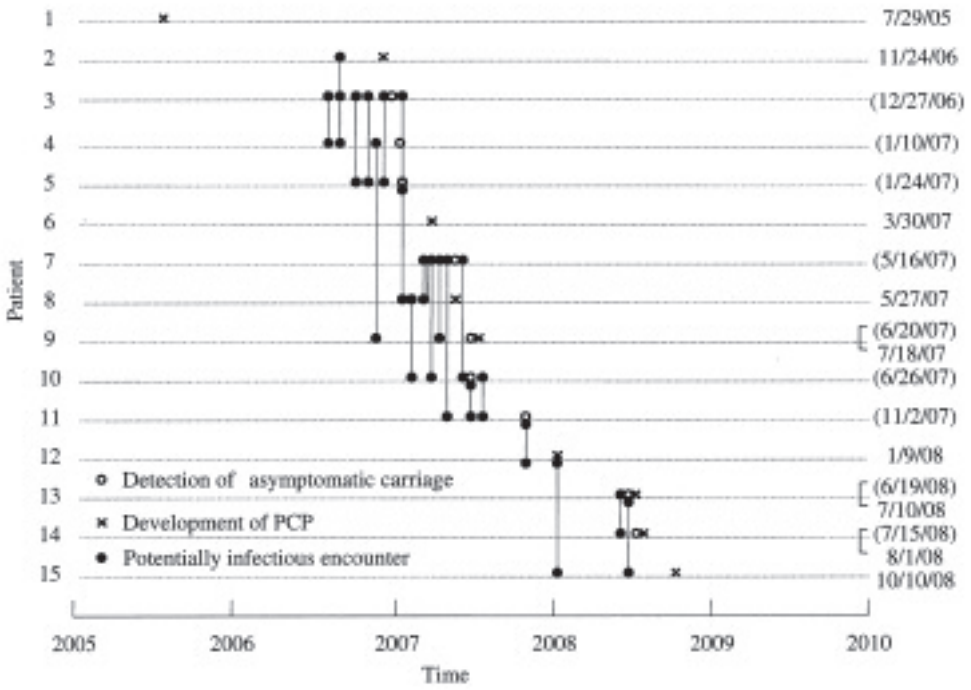

Figure 1. Transmission map of *P. jirovecii* among outpatients with RA. Black circles and lines represent potentially infectious encounters that are compatible with person-to-person transmission in our outpatient facility. Dates of visits with such encounters were: 8/2/06, cases 3 and 4; 8/30/06, cases 2-4; 10/4/06, cases 3 and 5; 11/1/06, cases 3 and 5; 11/22/06, cases 4 and 9; 11/29/06, cases 3 and 5; 1/24/07, cases 3, 5, and 8; 1/26/07, cases 8 and 10; 3/23/07, cases 7 and 8; 4/20/07, cases 7 and 8; 4/24/07, cases 7 and 10; 4/27/07, cases 7 and 9; 5/1/09, cases 7 and 11; 6/5/07, cases 7 and 10; 6/26/07, cases 10 and 11; 7/24/07, cases 10 and 11; 11/2/07, cases 11 and 12; 1/9/08, cases 12 and 15; 5/16/08, cases 13 and 14; 6/19/08, cases 13 and 15. Open circles and crosses represent detection of asymptomatic carriage of *P. jirovecii* and development of PCP, respectively. Numbers denote dates of these episodes (month/day/year) with dates enclosed in parentheses representing detection of asymptomatic carriage.

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2010. All rights reserved.

Downloaded on May 13, 2021 from www.jrheum.org

compromised individuals, some groups proposed the possible role of person-to-person transmission[4-6], while others suggested it may occur but does not constitute the major route of transmission[7,8]. The members of the cluster described here regularly visited the outpatient facility in our hospital. To investigate the possibility of encounters inside the hospital, dates of patients' visits were determined by reviewing their medical charts. As shown in Figure 1, we found that all the members, except cases 6 and 13, had potentially infectious encounters at the outpatient facility within at least 4 months before the first detection of *P. jirovecii*. In addition, case 6 was in the same inpatient ward awaiting surgery at the time when case 2 was hospitalized for PCP treatment. These data suggest that person-to-person transmission in hospital environments is a frequent event among RA outpatients who are receiving MTX. Cases 12 and 13 are a married couple and the latter developed PCP 6 months later. This leads us to believe that they may represent examples of interhuman transmission outside the hospital. No geographic clustering by postal code was noted, suggesting that a regional environmental source(s) outside the hospital was less likely.

Person-to-person transmission has been suggested as a possible mode of infection, even from immunocompetent persons transiently colonized by *P. jirovecii*, such as hospital staff members, to persons susceptible to PCP[9,10]. During the outbreak period described here, however, no positive results for the presence of *P. jirovecii* were obtained from the induced sputum of 42 healthy staff members who worked in the outpatient facility. Moreover, there was no occurrence of PCP among outpatients of other clinical sections who had shared the same outpatient facility with RA patients. These findings may suggest that RA outpatients with asymptomatic carriage can serve as an infectious reservoir for *P. jirovecii*, but its circulation is limited to this same patient group.

This is the first report to show a cluster of *P. jirovecii* infection among outpatients with RA. Hospital-acquired, person-to-person transmission was traceable in most cases within this cluster. Through the eradication of *P. jirovecii* from asymptomatic carriers and PCP patients, the outbreak was resolved. We hope that our experience encourages progress in understanding the potential role of asymptomatic carriers in the circulation of *P. jirovecii* among RA patients, which will allow us to undertake effective action to prevent and control future outbreaks.

SHUNSUKE MORI, MD, PhD, Clinical Research Center for Rheumatic Disease and Department of Rheumatology; ISAMU CHO, MD, PhD, Clinical Research Center for Rheumatic Disease and Division of Respiratory Medicine, Department of Medicine; MINEHARU SUGIMOTO, MD, PhD, Division of Respiratory Medicine, Department of Medicine, NHO Kumamoto Saishunsou National Hospital, Kumamoto, Japan. Address correspondence to Dr. Mori.
E-mail: moris@saisyunsou1.hosp.go.jp

REFERENCES

1. de Boer MG, Bruijnesteijn van Coppenraet LE, Gaasbeek A, Berger SP, Gelinck LB, van Houwelingen HC, et al. An outbreak of Pneumocystis jirovecii pneumonia with 1 predominant genotype among renal transplant recipients: interhuman transmission or a common environmental source? Clin Infect Dis 2007;44:1143-9.
2. Mori S, Cho I, Sugimoto M. A followup study of asymptomatic carriers of Pneumocystis jirovecii during immunosuppressive therapy for rheumatoid arthritis. J Rheumatol 2009;36:1600-5.
3. Mori S, Cho I, Ichiyasu H, Sugimoto M. Asymptomatic carriage of Pneumocystis jirovecii in elderly patients with rheumatoid arthritis in Japan: a possible association between colonization and development of Pneumocystis jirovecii pneumonia during low-dose MTX therapy. Mod Rheumatol 2008;18:240-6.
4. Yazaki H, Goto N, Uchida K, Kobayashi T, Gatanaga H, Oka S. Outbreak of Pneumocystis jirovecii pneumonia in renal transplant recipients: P. jirovecii is contagious to the susceptible host. Transplantation 2009;88:380-5.
5. Schmoldt S, Schuhegger R, Wendler T, Huber I, Sollner H, Hogardt M, et al. Molecular evidence of nosocomial Pneumocystis jirovecii transmission among 16 patients after kidney transplantation. J Clin Microbiol 2008;46:966-71.
6. Rabodonirina M, Vanhems P, Couray-Targe S, Gillibert RP, Ganne C, Nizard N, et al. Molecular evidence of interhuman transmission of Pneumocystis pneumonia among renal transplant recipients hospitalized with HIV-infected patients. Emerg Infect Dis 2004;10:1766-73.
7. Olsson M, Eriksson BM, Elvin K, Strandberg M, Wahlgren M. Genotypes of clustered cases of Pneumocystis carinii pneumonia. Scand J Infect Dis 2001;33:285-9.
8. Helweg-Larsen J, Tsolaki AG, Miller RF, Lundgren B, Wakefield AE. Clusters of Pneumocystis carinii pneumonia: analysis of person-to-person transmission by genotyping. QJM 1998;91:813-20.
9. Vargas SL, Ponce CA, Gigliotti F, Ulloa AV, Prieto S, Munoz MP, et al. Transmission of Pneumocystis carinii DNA from a patient with P. carinii pneumonia to immunocompetent contact health care workers. J Clin Microbiol 2000;38:1536-8.
10. Miller RF, Ambrose HE, Wakefield AE. Pneumocystis carinii f. sp. hominis DNA in immunocompetent health care workers in contact with patients with P. carinii pneumonia. J Clin Microbiol 2001;39:3877-82.

J Rheumatol 2010;37:7; doi:10.3899/jrheum.091294

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2010. All rights reserved.

Downloaded on May 13, 2021 from www.jrheum.org