Pneumocystis carinii Infection in a Renal Transplant Recipient
Presented as Walking Pneumonia Occurring 18 Years After Transplantation: A Case Report

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Abstract

Introduction: Pneumocystis carinii pneumonia remains a crucial cause of morbidity and mortality in organ transplant recipients. Pneumocystis carinii pneumonia occurs most frequently within the first 6 months post-transplant. Onset is generally fulminant, and typical symptoms include fever and productive cough accompanied with respiratory distress.

Case Presentation: Here, we present a case of a patient who developed P. carinii pneumonia 18 years after renal transplantation and referred to Taichung Veteran General hospital in Taiwan in September 2015. The disease course was indolent without hypoxemia and dyspnea, mimicking walking pneumonia. The risk factors in our case contributing to P. carinii pneumonia included increased doses of immunosuppressants due to recent rejection, treatment with tacrolimus rather than cyclosporine, lymphopenia, and possibly the occurrence of urothelial carcinoma, implying an immune-deficient state. The inflammatory response of P. carinii pneumonia was not intense and gave rise to an indolent disease course.

Conclusions: This case should remind clinicians that P. carinii pneumonia could present atypically in an indolent form many years following organ transplantation, especially when predisposing factors are present. Longer duration of P. carinii pneumonia prophylaxis, especially for high-risk patients such as those with potent immunosuppressive regimen, or those who received recent treatment for acute cellular or humeral rejection may be considered.

Keywords: Kidney Transplantation, Walking Pneumonia, Pneumocystis carinii Pneumonia

1. Introduction

Pneumocystis carinii pneumonia (PCP) continues to be a potential life-threatening pulmonary infection in organ transplant recipients. The period of greatest risk for PCP is the first 6 months after transplantation (1). The onset of PCP in patients without human immunodeficiency virus infection (non-HIV) usually involves a more rapid respiratory insufficiency than in human immunodeficiency virus (HIV) patients (2).

The predisposing factor for PCP in non-HIV patients is usually associated with cell mediated immunity impairment (3). For renal transplant recipients, treatment with tacrolimus or sirolimus, recent rejection, lymphopenia, older age, and cytomegalovirus (CMV) infection are associated with increased risk of PCP infection (1, 4, 5). Patients who received ABO-incompatible transplantation and those who were treated with belatacept are at a higher risk for PCP infection (6).

Here, we report a case of PCP in a renal transplant recipient with atypical presentation, with an indolent onset occurring 18 years after transplantation. The late onset and mild symptoms without hypoxemia resembling a walking pneumonia made this case different from other studies, reminding the clinical physicians that PCP could also present in such an indolent form in organ transplant recipients, especially when predisposing factors are present.

2. Case Presentation

A 57-year-old female with end-stage renal disease underwent a deceased donor kidney transplant 18 years prior to subsequent presentation with a fever, headache, and productive cough for 1 week.

Her medical history included hyperuricemia, hyperlipidemia, hypertension, and chronic use of analgesics. The kidney transplant was performed in 1997 in China, and she was subsequently followed up in Taichung Veteran General hospital in Taiwan. The initial immuno-suppressive regimen included cyclosporine, mycopheno-
late mofetil (MMF), and prednisolone. Trimethoprim-sulfamethoxazole (TMP-SMX) was prescribed for PCP prophylaxis during the 6 months post-transplantation. She was diagnosed with urothelial carcinoma (UC) in 2000. After transurethral resection of the bladder tumor, the cystourethroscopy done in 2005 revealed no tumor recurrence. Her renal function was relatively stable until 2012, after which serum creatinine increased to 2.2 mg/dL. Cyclosporine was replaced by Advagraf due to suspected transplant rejection. In October 2012, renal biopsy results revealed acute tubular injury suggestive of calcineurin inhibitor use. We decreased the dose of Advagraf and added sirolimus as of December 2012. In June 2014, the follow-up renal biopsy results showed mild acute T-cell mediated rejection. We titrated the dose of Advagraf to 3 mg per day to maintain the drug level at 3 - 5 ng/mL. The drug level of sirolimus was also approximately 3 - 5 ng/mL. Her serum creatinine was maintained at 2.5 - 3.2 mg/dL under the combination of Advagraf, MMF, sirolimus, and prednisolone treatment.

The patient complained of fever with productive cough lasting for 1 week in September 2015. She also experienced headache, sore throat, and general muscle soreness and was admitted to the Taichung Veteran General hospital in Taiwan on September 28, 2015. She was pyrexial with a temperature of 38.1°C. Her blood pressure was 110.70 mmHg, pulse rate 94/min, respiratory rate 16/min, and oxygen saturation on room air was 97%. Auscultation on the chest revealed crackles in bilateral basal lung fields.

Laboratory tests on September 28, 2015 revealed mild anemia with normal leukocyte and platelet counts. The absolute lymphocyte count was 0.68 × 10^9/L. The C-reactive protein level was 2.37 mg/dL (normal < 0.3 mg/dL), and the procalcitonin level was 0.6 ng/mL (normal < 0.5 ng/mL). The serum creatinine level was mildly elevated at 3.67 mg/dL. The lactate dehydrogenase level was elevated at 317 U/L (normal: 120 - 240 U/L). Arterial blood gas yielded PaO_2 at 146.4 mmHg, and SaO_2 was 99% under nasal cannula at 3 L/min. PaO_2/FiO_2 ratio was 443.6. Influenza rapid test yielded a negative result. The laboratory data are summarized in Table 1. Plain chest radiography results revealed bilateral pulmonary infiltration, predominantly in the lower lung field (Figure 1A). High resolution computed tomography (HRCT) of the lung field showed diffuse centrilobular nodules with tree-in-bud and some ground-glass opacities. Partial atelectasis with linear infiltration and traction bronchiectasis in the right middle lobe were found and accompanied with bilateral pleural effusion (Figure 1B).

Atypical pneumonia with bronchiolitis was considered. We checked for CMV by serum QPCR, *Mycoplasma pneumoniae*-specific IgM, *Legionella*-specific antibodies using immunofluorescence and *Aspergillus* by the galactomannan antigen test, and performed a latex test for *Cryptococcus* antigen; all revealed negative results. Sputum acid fast stain and quantiferon-tuberculosis (TB) assay were both negative. A pleural effusion study showed a lymphocyte predominant transudate and a negative bacterial and TB culture. Empirical antibiotics with ampicillin/sulbactam 1.5 g q12h and azithromycin 500 mg qd were prescribed. Sirolimus was discontinued. Three days later (October 1, 2015), productive cough improved but a low-grade fever persisted. A chest radiograph showed delayed resolution. The sputum cytology reported *Pneumocystis jirovecii* seen with periodic Schiff-methenamine silver staining on the 7th day of admission (Figure 2). We prescribed intravenous TMP-SMX at a dose of 80 - 400 mg 3 times a day according to the patient’s creatinine clearance. The low-grade fever subsequently resolved and a chest radiography, which was performed 2 weeks later, exhibited significant improvement of the bilateral reticulonodular infiltrations. After 2 weeks, TMP-SMX was administered orally to achieve a total of 3 weeks treatment. Throughout the disease course, she only had mild dyspnea on exertion, with preserved PaO_2/FiO_2 ratio.

### 3. Discussion

PCP is a major cause of morbidity and mortality in patients receiving immunosuppressant therapies. Patients with and without HIV infection may have differing presentations of PCP infection. PCP in HIV patients has a slow and progressive onset, accompanied with non-specific symptoms such as fever, non-productive cough, weight loss, and cachexia (7). In contrast, PCP in non-HIV patients usually presents with abrupt dyspnea, hypoxemia, and respiratory failure (2). The outcome of PCP in non-HIV patients is usually worse than that of HIV patients (8). A possible explanation for this observation is that the host inflammatory response is assumed to be more intense in non-HIV patients with PCP, and the extent of lung damage in PCP is thought to be determined by the host inflammatory response rather than the virulence of the infecting organism (9). This theory is in concordance with the study of Limper et al. (10), which indicated that the inflammatory response itself, rather than parasite number, correlated with more advanced disease.

Predisposing factors for PCP in non-HIV patients include cell mediated immunity impairment and glucocorticoid treatment (3). In the population of renal transplant recipients, treatment with tacrolimus is associated with a higher risk of PCP than cyclosporine (1). Sirolimus may increase the risk of PCP infection in renal transplant recipients (4). Iriart et al. discovered that lymphocyte count...
Figure 1. Chest Radiography and HRCT

A. Chest plain film revealed bilateral interstitial and alveolar infiltration with lower lung predominant. B. High resolution computed tomography (HRCT) of lung field showed diffuse centrilobular nodules with tree-in-buds and some ground-glass opacities in bilateral lungs. Partial atelectasis with linear infiltration and traction bronchiectasis in right middle lobe were found, accompanied with bilateral pleural effusion.

Figure 2. Sputum Cytology. Pneumocystis Carinii Seen with Periodic Schiff-Methenamine Silver Stain, × 400

was one of the most pertinent predictive criteria to evaluate the risk of PCP in organ transplant recipients (5). The risk factors in our case contributing to PCP included increased doses of immunosuppressants due to recent rejection, treatment with tacrolimus rather than cyclosporine, lymphopenia, and possibly the occurrence of UC, implying an immune-deficient state. Thus, the inflammatory response of PCP in this patient's condition was not as intense as in other non-HIV PCP cases and gave rise to an indolent disease course. Our patient was diagnosed of PCP by sputum cytology rather than bronchoalveolar lavage, which suggest a higher number of P. carinii organisms in the respiratory system. However, the inflammatory response was apparently milder. Taken together, we speculate that she may have had an indolent disease course despite higher numbers of parasite infestation, which is similar to infection in patients with HIV.

Compared with previous studies, our case was unique for the particularly late onset of PCP and an indolent disease course. Hardy et al. (11) found that PCP occurred more frequently in males, with 86% of the cases having an onset within the third or fourth months post renal transplantation. Another case control study revealed that PCP pneumonia occurred in a median of 18 months after renal transplantation (12), and graft rejection was the only risk factor in the multivariate model. Eitner et al. indicated that among all the 60 individual PCP cases, 52 cases (87%) were diagnosed within 1-year post-transplantation (13). PCP cases had a poorer renal function, more biopsy-proven rejections, and more frequent treatment with mycophenolate mofetil and less frequent treatment with interleukin-2 receptor antagonist. Li et al. reported a later onset (5 years after renal transplantation) and atypical presentation of PCP pneumonia (14). The case had an indolent onset of pneumonia, which was similar to our case. Extrapulmonary symptoms including body weight loss and diarrhea were found, but our case complained of headache,
Table 1. Clinical Characteristics and Laboratory Data of the Patient

| Characteristic                                      | Value               |
|----------------------------------------------------|---------------------|
| Age, y                                             | 57                  |
| Gender                                             | Female              |
| Time between PCP pneumonia and transplantation, mo | 216                 |
| TMP-SMX prophylaxis duration, mo                   | 6                   |
| Laboratory parameters                              |                     |
| White blood cell count, per mm$^3$                 | 4.2 (3.5 - 11.0)    |
| Lymphocyte %                                       | 16.4 (19 - 48)      |
| Hgb, g/dL                                          | 8.6 (12 - 16)       |
| Creatinine, mg/dL                                  | 3.67                |
| LDH, U/L                                           | 317 (220 - 240)     |
| CRP, mg/dL                                         | 2.37 (< 0.3)        |
| Procalcitonin, ng/mL                               | 0.6 (< 0.5)         |
| PaO$_2$, mmHg (under nasal cannula, 3 L/min)       | 146.4               |
| PaO$_2$/FiO$_2$                                    | 443.6               |
| Immunosuppressant drug levels                      |                     |
| FK506 level, ng/mL                                 | 2.9 (1 - 15)        |
| Sirolimus level, ng/mL                             | 4.65 (3 - 15)       |
| Serology, culture, cytology                        |                     |
| Influenza rapid test                               | Negative            |
| CMV viremia, QPCR                                  | Negative            |
| Legionella-specific antibody                        | Negative            |
| Mycoplasma pneumonia IgM                           | Negative            |
| Quantiferon-tuberculosis (TB) assay                 | Negative            |
| Bacterial and TB culture of sputum                  | Negative            |
| Cytology of sputum                                 | Periodic Schiff-methenamine silver staining: Pneumocystis jiroveci |

sore throat, and general muscle soreness. Both cases had a recent rejection episode.

Our patient received TMP-SMX for 6 months after kidney transplantation for PCP prophylaxis. The Kidney Disease Improving Global Outcomes Guideline recommends PCP prophylaxis for 3 to 6 months after kidney transplantation, whereas the American Society of Transplantation recommends 6 to 12 months (15, 16). PCP occurs most frequently within the first 6 months post-transplant. However, late onset PCP beyond 12 months is occasionally seen (17). In our case, PCP occurred after an acute T-cell rejection episode 18 years post-transplantation. Therefore, some transplant centers use longer duration of PCP prophylaxis, especially for high risk patients such as those with potent immunosuppressive regimen or recent treatment for acute cellular or humeral rejection (17). For lung and small bowel transplant recipients, as well as those with a history of PCP infection or CMV disease, lifelong prophylaxis for PCP may be considered (16).

Chest radiographic finding of PCP may be nonspecific, and HRCT may provide further information. Extensive ground-glass opacity noted on the HRCT scan is the principle finding in PCP. Compared to HIV patients, a more rapid spread ground-glass opacity representing alveolitis and less formation of cyst lesions were shown to be the typical findings in non-HIV PCP infection (18). Centrilobular nodules, thickened interlobular septal lines, and tree-in-bud corresponding to bronchiolitis are sometimes present in non-HIV PCP infections (19). In our case, there were diffuse centrilobular nodules with tree-in-bud lesions. Ground-glass opacity was not extensive. The image findings were compatible with the relatively indolent disease course.

The limitations of this case study were as follow: Firstly, the patient had a partial improvement of productive cough after empirical antibiotics with ampicillin/sulbactam and azithromycin. Although sputum culture yielded negative results, there was still the possibility of coinfection with bacterial pneumonia or atypical pneumonia. Secondly, polymerase chain reaction (PCR) of respiratory fluid for the diagnosis of PCP was not available at our center. Advantages of PCR includes diagnosis of PCP pneumonia with negative sputum or bronchoalveolar lavage smears although PCR cannot distinguish between colonization and disease.

We reported a case of PCP, which occurred 18 years post-transplantation, in a renal transplant recipient. The clinical course was indolent without significant hypoxemia, resembling walking pneumonia. This case should act as a reminder to clinical physicians that PCP can present in an indolent form in organ transplant recipients, especially when predisposing factors were present including recent rejection episodes, increased doses of immunosuppressant drugs, lymphopenia, and long-term corticosteroid use.

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Footnotes

Authors’ Contribution: Hsien-Fu Chiu drafted the article and involved with patient care. Mei-Chin Wen contributed...
the manuscript and involved with pathology report. Kuo-Hsiung Shu drafted, revised the article, and was involved with patient care.

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**References**

1. Luft V, Kliem V, Behrend M, Pichlmayr R, Koch KM, Brunkhorst R. Incidence of Pneumocystis carinii pneumonia after renal transplantation. Impact of immunosuppression. *Transplantation*. 1996;62(1):421-3. doi: 10.1097/00007890-199601050-00022. [PubMed: 8779695].

2. Nuesch R, Bellini C, Zimmerli W. Pneumocystis carinii pneumonia in human immunodeficiency virus (HIV)-positive and HIV-negative immunocompromised patients. *Clin Infect Dis*. 1999;29(6):1509-23. doi: 10.1086/313534. [PubMed: 10585806].

3. Rodriguez M, Fishman JA. Prevention of infection due to Pneumocystis spp. in human immunodeficiency virus-negative immunocompromised patients. *Clin Microbiol Rev*. 2004;17(4):770-82. doi: 10.1128/CMR.17.4.770-782.2004. [PubMed: 15489347].

4. Neff RT, Jindal RM, Yoo DY, Hurst FP, Agodoa LY, Abbott KC. Analysis of USRDS: incidence and risk factors for Pneumocystis jiroveci pneumonia. *Transplantation*. 2009;88(1):31-41. doi: 10.1097/TP.0b013e3181b8aad256. [PubMed: 19584699].

5. Iriart X, Challan Belval T, Fillaux J, Esposito L, Lavergne RA, Cardeau-Desangles I, et al. Risk factors of Pneumocystis pneumonia in solid organ recipients in the era of the common use of posttransplantation prophylaxis. *Am J Transplant*. 2015;15(1):190-9. doi: 10.1111/aajt.12947. [PubMed: 25496995].

6. Brakemeier S, Durr M, Bachmann F, Schmidt D, Gaedke J, Budde K. Risk Evaluation and Outcome of Pneumocystis jiroveci Pneumonia in Kidney Transplant Patients. *Transplant Proc*. 2016;48(9):2924-30. doi: 10.1016/transpro.2016.05.017. [PubMed: 2792109].

7. Kales CP, Murren JR, Torres RA, Crocco JA. Early predictors of in-hospital mortality for Pneumocystis carinii pneumonia in the acquired immunodeficiency syndrome. *Arch Intern Med*. 1987;147(8):1413-7. doi: 10.1001/archinte.147.8.1413. [PubMed: 315209].

8. Magne D, Angoulvant A, Botterel F, Bouges-Michel C, Bougnoux ME, Bourree P, et al. Pneumocystosis: a network survey in the Paris area 2003-2008. *Eur J Clin Microbiol Infect Dis*. 2011;30(5):673-5. doi: 10.1007/s10096-010-1139-0. [PubMed: 21229281].

9. Chen CS, Zheng SL, Fang ZX, Li YP, Ye M, Zhang DQ, et al. [Alveolar damage of pneumocystosis carinii pneumonia in renal transplantation recipients]. *Zhonghua jie He He Hu Xi Za Zhi*. 2004;27(3):161-4. [PubMed: 15150325].

10. Limper AH, Offord KP, Smith TF, Martin WJ. Pneumocystis carinii pneumonia. Differences in lung parasite number and inflammation in patients with and without AIDS. *Am Rev Respir Dis*. 1989;140(5):1204-9. doi: 10.1164/ajrccm.140.5.1204. [PubMed: 2817582].

11. Hardy AM, Wajszzczuk CP, Suffredini AF, Hakala TR, Ho M. Pneumocystis carinii pneumonia in renal-transplant recipients treated with cyclosporine and steroids. *J Infect Dis*. 1984;149(2):143-7. [PubMed: 6128666].

12. De Castro N, Xu F, Porcher R, Pavie J, Molina JM, Peraldi MN. Pneumocystis jirovecii pneumonia in renal transplant recipients occurring after discontinuation of prophylaxis: a case-control study. *Clin Microbiol Infect*. 2009;15(9):1375-7. doi: 10.1111/j.1469-0691.2009.03143.x. [PubMed: 20041898].

13. Eitner F, Hauser IA, Rettkowski O, Rath T, Lopau K, Pliquet RU, et al. Risk factors for Pneumocystis jiroveci pneumonia (PcP) in renal transplant recipients. *Nephrol Dial Transplant*. 2011;26(6):2013-7. doi: 10.1093/ndt/gfr689. [PubMed: 21675445].

14. Li JY, Yong TY, Grove DI, Coates PT. Late-onset and atypical presentation of Pneumocystis carinii pneumonia in a renal transplant recipient. *Clin Exp Nephrol*. 2009;13(3):92-5. doi: 10.1007/s10157-008-0079-9. [PubMed: 18758701].

15. Kasiske BI, Zeier MG, Chapman JR, Craig JC, Ekberg H, Garvey CA, et al. KDIGO clinical practice guideline for the care of kidney transplant recipients: a summary. *Kidney Int*. 2010;77(4):299-311. doi: 10.1038/ki.2009.377. [PubMed: 19847756].

16. Martin SI, Fishman JA, A. S. T. Infectious Diseases Community of Practice . Pneumocystis pneumonia in solid organ transplantation. *Am J Transplant*. 2013;13 Suppl 4:272-9. doi: 10.1111/aajt.12189. [PubMed: 23465020].

17. Perez-Ordono L, Hoyo I, Sanclemente G, Ricart MJ, Cofan F, Perez-Villa F, et al. Late-onset Pneumocystis jirovecii pneumonia in solid organ transplant recipients. *Transpl Infect Dis*. 2014;16(2):324-8. doi: 10.1111/tid.12184. [PubMed: 24456244].

18. Hardak E, Brook O, Yigla M. Radiological features of Pneumocystis jiroveci pneumonia in immunocompromised patients with and without AIDS. *Lung*. 2001;179(2):159-64. doi: 10.1007/s10434-001-0014-4. [PubMed: 11249649].

19. Roux A, Gonzalez F, Roux M, Mehrad M, Menotti J, Zahar J, et al. Update on pulmonary Pneumocystis jiroveci infection in non-HIV patients. *Med Mal Infect*. 2014;44(5):185-98. doi: 10.1016/j.medmal.2014.01.007. [PubMed: 24610595].