Case Report

Pneumocystis carinii Pneumonia Among Renal Transplant Recipients Despite Antibiotic Prophylaxis

Sze-Kit Yuen, Ka-Fai Yim, Yuen-Fun Mak,[1] Kwok-Hong Chu, Hon-Lok Tang, Ka-Shun Fung, Wai-Han Chan, Kwok-Lung Tong

Pneumocystis carinii pneumonia (PCP) is a well-known opportunistic infection in renal transplant recipients; it is associated with high mortality, mostly within the first 6 months post-transplantation. The disease has been effectively prevented by routine antibiotic prophylaxis. Recently, however, we encountered three consecutive cases of PCP; one developed the disease at 8 months and another at 11 months post-transplantation. An overall assessment of a patient's degree of immunosuppression is essential when considering the duration of PCP prophylaxis. Instead of the routine regimen of 6 months, 1-year PCP prophylaxis may be required for those who are on both tacrolimus and mycophenolate mofetil. [*Hong Kong J Nephrol* 2005;7(2):93–6]

Key words: co-trimoxazole, *Pneumocystis carinii*, prophylaxis, renal transplantation

Pneumocystis carinii 肺炎 (PCP) 是發生於腎臟移植接受者的伺機感染之一，具有高死亡率，特別是在移植術後的 6 個月內；臨床上可採用預防性抗生素加以防範。然而，最近在本院卻連續出現 3 宗 PCP 的個案，其中兩宗分別於移植術後 8 及 11 個月發生。本文指出，PCP 預防性療程持續時間的決定，必須考慮到病人所受到的免疫抑制的程度。對於同時接受 tacrolimus 及 mycophenolate mofetil 的病人，可能有必要將 PCP 預防性療程從 6 個月延長至 1 年。

Introduction

Pneumocystis carinii pneumonia (PCP) is a disease that causes severe alveolar damage [1] and which has a high mortality rate [2,3]. It is a well-recognized opportunistic infection among renal transplant recipients [4]; approximately 5% of those not taking antibiotic prophylaxis develop PCP [5]. It usually occurs 3–6 months after renal transplantation [6–9], although it can appear as late as 9 years after [10].

Centers using the regimens of co-trimoxazole (trimethoprim-sulfamethoxazole, TMP-SMX) prophylaxis for the initial 4 months [11] or 6 months [8] reported no subsequent PCP cases. Indeed, it should now be standard practice to prescribe PCP prophylaxis in all renal transplant recipients, with co-trimoxazole being the drug of choice [4]. Our center implemented routine PCP prophylaxis for all renal transplant recipients in 1993. The majority of our patients receive oral co-trimoxazole (TMP-SMX 80 mg/400 mg) for 6 months. Only isolated cases of PCP have been diagnosed since 1993, notably in transplant recipients who are either noncompliant or contraindicated to co-trimoxazole prophylaxis. Over a period of 3 months, however, we encountered three cases of PCP. Of note, two of these patients developed PCP more than 8 months post-transplantation, when they had already been taken off their PCP prophylaxis.

Case Reports

Case 1

A 49-year-old man with a past history of IgA nephropathy was diagnosed with end-stage renal failure requiring hemodialysis in 1997. In November 2004, he underwent cadaveric renal transplantation in Mainland China. Induction immunosuppressives included steroid, tacrolimus, mycophenolate mofetil (MMF) and daclizumab. Postoperatively, he had been treated with

Renal Unit, Department of Medicine and Geriatrics, and [1]Department of Pathology, Princess Margaret Hospital, Hong Kong SAR, China.
Address correspondence and reprint requests to: Dr. Yuen Sze Kit, Renal Unit, Department of Medicine and Geriatrics, Princess Margaret Hospital, 2–10 Princess Margaret Hospital Road, Lai Chi Kok, Kowloon, Hong Kong SAR, China.
Fax: (+852) 2741-0752; E-mail: skit@alumni.cuhk.net

pulse doses of steroids for presumed acute rejection without histologic proof. His renal function was normal when he returned to Hong Kong. We started him on oral co-trimoxazole 480 mg daily as PCP prophylaxis, but he did not take it regularly.

He presented on 27th February 2005 (approximately 3 months post-renal transplantation) with a 1-week history of low-grade fever and shortness of breath. At that time, his immunosuppressives included prednisolone 10 mg om, tacrolimus 1 mg om and 0.5 mg pm, and MMF 500 mg bd. He was also on diltiazem 30 mg tds, and his latest tacrolimus trough level was 9.9 μg/L.

Chest X-ray on admission showed bilateral lower zone infiltrates. MMF was stopped and he was empirically started on intravenous co-trimoxazole, ganciclovir and piperacillin/tazobactam. Transbronchial biopsy and bronchoalveolar lavage the next day confirmed PCP. High-dose intravenous steroid was added. He ran a stormy course requiring prolonged mechanical ventilation (Figure). Tacrolimus was stopped. His clinical course was further complicated by noninvasive pulmonary aspergillosis, asymptomatic cytomegalovirus pp65 antigenemia, ganciclovir-related bone marrow suppression and pseudomonas pneumonia; all were finally overcome. He was discharged 7 weeks after admission with fair exercise tolerance and normal renal function.

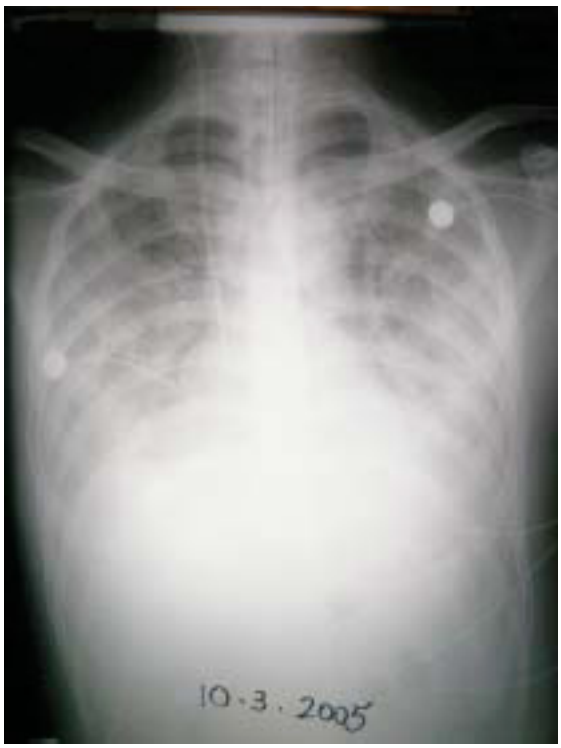

Figure. Case 1: chest X-ray on day 12 of hospitalization shows bilateral diffuse lung field haziness due to *Pneumocystis carinii* pneumonia.

Case 2

A 60-year-old man with a past history of hypertension, polycystic kidney disease and chronic renal failure underwent pre-emptive cadaveric renal transplantation in Mainland China in August 2004. No antibody was used at induction. He completed a 6-month course of oral co-trimoxazole 480 mg as PCP prophylaxis. He did not experience any rejection or infective episode, and he had normal renal function.

On 2nd May 2005 (approximately 8 months post-transplantation), he was hospitalized for cough, productive sputum and low-grade fever. His immunosuppressives included prednisolone 7.5 mg daily, tacrolimus 3 mg om and 2.5 mg pm, and MMF 500 mg bd. His latest tacrolimus trough level was 10.1 μg/L.

His white cell count was 5.9×10^9/L with relative neutrocytosis (82.2%). Chest X-ray showed left lower zone haziness. MMF was stopped and intravenous amoxicillin-clavulanate and oral clarithromycin started. His fever subsided and he remained clinically stable for the next 5 days. His sputum culture yielded *Flavobacterium* spp. Antibiotics were switched to levofloxacin according to sensitivity.

Over the next 3 days, he became febrile again and required up to 6 L/min oxygen. Chest X-ray confirmed progression of lower zone consolidation. Intravenous piperacillin/tazobactam and co-trimoxazole were added. Bronchoalveolar lavage and transbronchial lung biopsy confirmed PCP. He required noninvasive positive pressure ventilation (NIPPV) temporarily, and was discharged 5 weeks after hospitalization with normal renal function and exercise tolerance.

Case 3

A 52-year-old man with a history of end-stage renal failure due to hypertensive nephropathy underwent cadaveric renal transplantation in June 2004 in Mainland China. No antibody induction was used. He suffered one episode of Banff class IA acute cellular rejection in August 2004, which was partially reversed by pulse methylprednisolone. Creatinine level stabilized at around 200 μmol/L thereafter. He completed a standard 6-month course of co-trimoxazole PCP prophylaxis.

He presented on 9th May 2005 (approximately 11 months post-transplantation) for cough and fever. His immunosuppressives included prednisolone 10 mg om, tacrolimus 4 mg bd, and MMF 750 mg bd. His latest tacrolimus trough level was 7.8 μg/L.

He was started on levofloxacin for right lower lobe pneumonia, which was confirmed by chest X-ray. MMF was stopped. He discharged himself against medical advice the next day but continued to take oral levofloxacin. He presented with shortness of breath 3 days later, and chest X-ray showed progression of

consolidation to the right lower lobe as well. Antibiotics were changed to piperacillin/tazobactam and azithromycin. Despite this, he deteriorated rapidly and required mechanical ventilation. Bronchoalveolar lavage confirmed the diagnosis of PCP. Tacrolimus was stopped and intravenous co-trimoxazole and steroids started. His clinical course was complicated by unilateral pneumothorax, acute renal failure, recurrent line sepsis and fungemia. He died 8 weeks after hospitalization.

Discussion

Case clustering and possible nosocomial transmission of *Pneumocystis carinii* has been reported in renal transplant recipients in their early post-transplantation period [12]. It is unusual to encounter three cases of PCP within such a short period of time (3 months), but apparently, our three patients did not have direct contact with one another prior to symptom onset. Genotyping of the organism was not performed, so a definite epidemiologic link could not be established. Nevertheless, exposure to a common hospital environment reservoir cannot be ruled out.

PCP prophylaxis failures may be due to noncompliance to chemoprophylaxis and recent intensified immunosuppression [12]. Case 1 had similar reasons for failure. Other reasons for prophylaxis failure [13] include sulfonamide resistance related to mutation of dihydropterate synthase [14].

Cases 2 and 3 are special in that they developed PCP during the late transplantation period (i.e. > 8 months post-transplantation), when they were on relatively low-dose immunosuppression and PCP prophylaxis had stopped. To our knowledge, late PCP in renal transplant recipients has not been reported in Hong Kong. It is interesting to note that all of these three patients were on both tacrolimus and MMF. Their high immunosuppressive potential [9,15] probably explains the higher risks of infectious complications.

The duration of co-trimoxazole prophylaxis given by different renal transplant centers varies from a few months to more than 12 months [16,17]. The recognized cross-resistance between components of co-trimoxazole and sulfadoxine/pyrimethamine means that its prolonged use promotes selection of drug-resistant *Plasmodium falciparum* [18,19] and emergence of resistant bacteria [14]. Therefore, although PCP has a mortality rate of up to 37% [2], adopting a practice of routine lifelong prophylaxis [20] is probably unwise.

When considering the duration of PCP prophylaxis, transplant centers should adopt an individualized approach. We believe the overall degree of immunosuppression [21], rather than any single immunosuppressive agent, to be predictive of the risk of PCP development. Those who have been given high-dose pulse steroids, T cell depleting antibody, potent immunosuppressive regimen (i.e. concomitant use of tacrolimus and MMF) and who are elderly [22] are particularly at risk; a prolongation of PCP prophylaxis up to 1 year is probably warranted in these individuals.

In conclusion, we reported three consecutive cases of PCP within a 3-month period in our renal unit. Late presentation of PCP is possible in this era of heavy immunosuppression. An individualized approach should be adopted when deciding the duration of PCP prophylaxis. Oral co-trimoxazole for 1 year is probably appropriate for those taking both tacrolimus and MMF.

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