Late-onset and atypical presentation of *Pneumocystis carinii* pneumonia in a renal transplant recipient

Jordan Y. Z. Li · Tuck Y. Yong · David I. Grove · P. Toby H. Coates

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Abstract *Pneumocystis jivorecii* (formerly known as *carinii*) pneumonia (PCP) is potentially a life-threatening opportunistic infection after organ transplantation, occurring most frequently in the first 12 months, where the incidence rate is several-fold higher than in later years. PCP typically presents with fever, cough, dyspnoea and hypoxia. In organ transplant recipients, the onset of symptoms is generally more fulminant compared to patients infected with the human immunodeficiency virus. We present a patient who developed PCP five years after a renal transplantation. His presentation was characterised by atypical symptoms and an indolent onset. Previous acute vascular rejection, ongoing maintenance prednisolone usage, cytomegalovirus seropositivity and past tuberculous infection may have predisposed this patient to PCP.

Keywords *Pneumocystis jivorecii* pneumonia · Kidney transplant · Immunosuppression · Opportunistic infection

Introduction

*Pneumocystis jirovecii* (formerly known as *carinii*) pneumonia (PCP) is a rare but life-threatening opportunistic infection which occurs in immunocompromised individuals such as organ transplant recipients. The incidence of PCP is highest in the first 12 months after transplantation, resulting in the use of trimethoprim-sulphamethoxazole (TMP-SMX) routinely during this period for primary prophylaxis [1]. As a result, the overall frequency of PCP has declined. PCP can still occur after the first 12 months, but at a very low incidence [2]. Although respiratory symptoms, hypoxia and pulmonary infiltrates on chest X-ray are the hallmarks of PCP, the presentation can sometimes be nonspecific [3]. We present a case of PCP occurring five years after renal transplantation with atypical presenting symptoms.

Case report

A 47-year-old Aboriginal man who received a living-related donor’s kidney allograft five years prior to this presentation was admitted to investigate a marked weight loss of 20 kg over six months with associated intermittent non-bloody diarrhoea. He had no symptoms of fever, dyspnoea, cough or haemoptysis. His medical history included end-stage renal disease due to Goodpasture’s Syndrome, previous pulmonary tuberculosis, coronary heart disease, hypertension and hyperlipidaemia. He was a
current smoker, with 35 pack-years of smoking. There were two mismatches between donor and recipient (one in locus A and one in locus B). Pre-transplant, he was IgG sero-positive for cytomegalovirus (CMV). He developed early acute vascular rejection post-transplant, which was successfully treated with a course of monoclonal anti-CD3 antibody (OKT3). He received prophylactic TMP-SMX for six months. His maintenance immunosuppressive therapy included tacrolimus 1 mg twice a day, sirolimus 1 mg daily and prednisolone 5 mg daily.

On initial physical examination, he weighed 59 kg, was apyrexial and not in respiratory distress. His blood pressure was 108/80 mmHg, pulse rate was 86/min, respiratory rate was 20/min and oxygen saturation (SaO₂) on room air was 94%. Auscultation of the chest revealed crackles in the right lung base. The remainder of the physical examination was noncontributory.

Admission laboratory tests revealed mild anaemia but normal leucocyte and platelet counts. The absolute lymphocyte count was 0.45 × 10⁹/L. Serum urea and creatinine were stable at concentrations of 9.4 mmol/L (RR: 2.7–8.0) and 143 μmol/L (50–120), respectively. C-reactive protein was 53 mg/L (<10), albumin was 29 g/L (34–48) and lactate dehydrogenase was 307 U/L (110–230). Glucose, bilirubin and liver function were all normal. Trough tacrolimus and sirolimus levels were 8.7 and 7.7 μg/L, respectively. Human immunodeficiency virus (HIV) status was negative. The chest X-ray (Fig. 1) revealed bilateral hazy opacity which was more prominent on the right lung. Small bilateral pleural effusion was also present. Computed tomography (CT) of the chest (Fig. 2) showed patchy ground glass opacity involving both lower lobes, multiple nodules throughout both lungs and background emphysematous changes, but no enlarged lymph nodes. The initial differential diagnosis included reactive tuberculosis, atypical pneumonia caused by CMV or fungal agents, and lung cancer.

After informed consent, an urgent bronchoscopy with bronchoalveolar lavage and transbronchial biopsy of the left lower lobe was performed. After bronchoscopy, his respiratory condition deteriorated and arterial blood gas taken while on 9 L/min of oxygen revealed pH 7.40, pCO₂ 24 mmHg, pO₂ 69 mmHg, bicarbonate 24 mmol/L and SaO₂ of 91%. As a result, he required noninvasive ventilation for 24 h.

No bacteria were cultured from the lavaged fluid, cultures for Mycobacterium tuberculosis and fungi were negative, and rapid CMV antigen test and blood CMV polymerase chain reaction (PCR) quantitative viral load were negative. However, the biopsy revealed areas of organising pneumonia and the presence of numerous P. jirovecii, confirmed by methenamine-silver staining, but PCR was not performed.

He was treated with intravenous TMP-SMX 160–800 mg four times a day and high-dose prednisolone 40 mg twice a day initially. Sirolimus was discontinued. TMP-SMX was changed to oral administration (160–800 mg three times a day) after three days of intravenous therapy. His renal function deteriorated further, with serum creatinine peaking at 245 μmol/L, and this was attributed to the effect of trimethoprim on the serum creatinine level. As a result graft biopsy was not performed.

The patient continued to improve with a slow resolution of the radiological abnormalities, and his diarrhoea settled after stopping sirolimus. He was discharged after three weeks in hospital. On discharge, his immunosuppression therapy consisted of tacrolimus 1.5 mg twice a day and prednisolone 20 mg daily. After the reduction of the TMP-SMX dose to the prophylaxis dose, serum creatine decreased to 168 μmol/L. Five months after discharge, he had regained 10 kg in weight and had no persistent respiratory symptoms. He remained on TMP-SMX 160–800 mg twice a week for secondary prophylaxis and the prednisolone dose has been reduced to 5 mg daily. One year after the PCP pneumonia, prophylactic TMP-SMX was ceased, and serum creatinine returned to 154 μmol/L.
Discussion

PCP is a well-recognised, serious opportunistic infection in solid organ transplant recipients and is associated with a high mortality rate that ranges between 29 and 50% in kidney transplant recipients [2, 4]. Prior to the introduction of primary prophylaxis with TMP-SMX, the incidence of PCP has been reported to be approximately 5% during the first six months after transplantation [2]. With the generalised use of TMP-SMX, the incidence of this infection has diminished, and was reported to be less than 2% in one study [2]. We report a case of PCP in a patient presenting with atypical symptoms five years after kidney transplantation.

Although PCP may be suspected when patients present with the classic triad of respiratory symptoms, hypoxia and diffuse radiographic abnormality, the presentation can sometimes be nonspecific, as seen in this case [3]. PCP in HIV-negative patients tends to have a shorter duration of symptoms and a lower frequency of nonspecific clinical features (e.g. sweating, weight loss and cachexia) [5]. In contrast, the most prominent symptom in the current case was weight loss that persisted over a protracted period of time. This case serves to remind clinicians involved with the care of transplant recipients that PCP can present atypically and that a high index of suspicion is required to ensure prompt diagnosis.

The vast majority of PCP occurs in the first six months after transplantation. After the first year, this infection is rare, with an incidence of 0.5% per 1,000 person transplant-years [2]. As a result, the current practice in our centre and most others is for prophylactic TMP-SMX to be administered for the first 12 months after transplantation. Debate persists as to whether prophylaxis should be continued beyond the first 12 months. Potential development of antibiotic resistance, side effects of therapy and the relatively low incidence after 12 months of transplantation argue against long-term prophylaxis. In contrast to the HIV-positive population, a single parameter like the CD4 + T cell count is lacking in non-HIV infective patients to help predict the individual at risk of PCP. The standard regimen, duration and validity for secondary prophylaxis in non-HIV infected patients have not been well studied. Secondary prophylaxis with careful monitoring of adverse reactions to TMP-SMX has been recommended [15].

Factors predisposing renal transplant recipients to late-onset PCP remain unknown, as it is such an uncommon infection after the first year. Without taking into account the timeframe of infection, several risk factors for PCP in renal transplantation have been reported in several studies. These include long-term corticosteroid therapy, the number and type of rejection treatments, usage of polyclonal/monoclonal antilymphocyte antibodies and immunomodulating infections such as CMV, tuberculosis and hepatitis C [2, 6, 7]. The case described had several risk factors, including previous CMV infection and tuberculosis, prednisolone usage since transplantation, and one previous episode of vascular rejection which was treated with OKT3. It is still not known why previous CMV or M. tuberculosis infections may predispose to PCP infections, even many years later.

Retrospective studies have suggested that the risk of PCP increases with the intensity of maintenance immunosuppression [8, 9]. In one report, the incidence of PCP increased from 1% in patients treated with cyclosporine to 14% among those receiving tacrolimus [9]. Sirolimus may increase the susceptibility to PCP in renal transplant recipients [10, 11]. In contrast, mycophenolate mofetil (MMF) may be protective against PCP. Clinically none of the patients who received MMF in the three initial studies developed PCP, compared to 2% of patients in control groups receiving azathioprine or placebo [12–14].

Glucocorticosteroids have a beneficial effect for PCP in patients with HIV infection. They reduce the inflammatory response of the alveolitis, resulting in clinical improvement; they reduce the need for mechanical ventilation and they reduce mortality without increasing the risk of other opportunistic infections [16]. Preliminary data suggest that high-dose adjunctive corticosteroids may accelerate recovery (shorter duration of mechanical ventilation, ICU and hospital admission) in non-HIV patients with PCP. However, evidence from randomised controlled trials is still lacking [17].
In summary, the diagnosis of PCP in renal transplant recipients remains a challenge, and awareness of atypical features is likely to facilitate early diagnosis and commencement of specific treatment. As seen in the current case, PCP can occur in a small number of renal transplant recipients, even several years after the transplantation. The presence of predisposing factors like long-term corticosteroid use, previous rejection episodes, previous CMV infection and tuberculosis should raise the possibility of PCP in a renal transplant recipient with respiratory or nonspecific symptoms.

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References