

A diagnosis not to forget in a long-term kidney transplant – *Pneumocystis jiroveci* pneumonia

Um diagnóstico a não esquecer em doentes transplantados renais de longa data – Pneumonia por *pneumocystis jiroveci*

Cláudia Bento¹, La Salette Martins², Manuela Almeida², Sofia Pedrosa², Leonídeo Dias², António Castro Henriques², António Cabrita²

¹ Department of Nephrology, Centro Hospitalar de Trás-os-Montes e Alto Douro. Vila Real, Portugal.

² Department of Nephrology, Hospital Geral de Santo António. Porto, Portugal.

Received for publication: 02/05/2014

Accepted in revised form: 08/08/2014

■ ABSTRACT

Potential aetiologies of infection in kidney transplant patients are diverse, ranging from common community-acquired infectious diseases to uncommon opportunistic infections. *Pneumocystis jiroveci* is a well-known opportunistic fungus that can cause life-threatening pneumonia in kidney transplant patients mostly within the first 6 months post-transplantation. This entity may occur after one year post-transplant, but the rate is very low. High immunosuppression, cytomegalovirus infection, previous history of acute rejection and poor GFR are risk factors for the occurrence of pneumocystis pneumonia (PCP) in kidney transplant patients. The treatment of choice is high-dose trimethoprim-sulfamethoxazol (TMP-SMX), reduction of immunosuppressive therapy and, in severe cases (defined by PaO₂ < 70 mmHg or an arterial-alveolar gradient > 35 mmHg), association with steroids. We report a case of PCP 12.5 years after renal transplant. A 51-year-old male presented to the hospital with a 3-day history of asthenia, fever and genitourinary complaints. Despite the initial treatment for cystitis he kept fever (> 38.5°C) and developed dry cough, hypoxaemia and rapidly progressive dyspnea. Physical examination revealed increased respiratory rate, tachycardia, cyanosis, wheezing and crackles on pulmonary auscultation. Radiographic alterations showed a bilateral interstitial infiltrates (not present on admission). On the 3th day, he was transferred to the intensive care unit and started non-invasive ventilation. The diagnosis was established by the identification of *Pneumocystis jiroveci* in bronchoalveolar lavage. Treatment was made with high-dose intravenous TMP-SMX plus steroids and resulted in clinical improvement of the symptoms and complaints.

Early diagnosis and prompt administration of empiric antimicrobial therapy are the cornerstones of successful treatment since the disease is associated with high mortality rate. This diagnosis should never be forgotten.

Key words: Fever; high immunosuppression; kidney transplant; *Pneumocystis jiroveci* pneumonia; respiratory failure.

RESUMO

Complicações infecciosas nos doentes transplantados renais são diversas e ocorrem quer por microrganismos habituais, quer por microrganismos oportunistas. *Pneumocystis jiroveci*, fungo oportunista, pode provocar pneumonia ameaçadora à vida nos doentes transplantados renais principalmente nos primeiros 6 meses após o transplante renal. Esta infeção pode ocorrer 1 ano após o transplante renal, mas a sua frequência é muito baixa. Elevada dose de imunossupressão, infeção por citomegalovirus, rejeição aguda e baixa taxa de filtração glomerular são fatores de risco para o desenvolvimento de pneumonia por pneumocystis nos doentes transplantados renais. O tratamento de escolha é realizado com doses elevadas de trimetoprim-sulfametoxazol, redução da dose de imunossupressão e em casos de severidade (definido: PaO₂ < 70 mmHg ou gradiente arterio-alveolar > 35 mmHg), associação com esteroides é recomendada. Apresentamos o caso de pneumonia por pneumocystis jiroveci, 12,5 anos após o transplante renal. Doente do sexo masculino de 51 anos que recorreu ao hospital por astenia, febre e queixas geniturinárias com 3 dias de evolução. Apesar do tratamento inicial para a cistite ele manteve febre (> 38,5°C) e desenvolveu de novo tosse seca, hipoxemia e dispneia súbita. Ao exame físico a realçar taquicardia, cianose, sibilos e crepitações na auscultação pulmonar. Alterações radiográficas a demonstrar infiltrado intersticial bilateral (não presente aquando da admissão). Transferido ao 3º dia para a unidade de cuidados intensivos para início de ventilação não invasiva. O diagnóstico foi realizado pelo isolamento de pneumocystis jiroveci no lavado broncoalveolar. O tratamento foi realizado com doses elevadas de trimetoprim-sulfametoxazol endovenoso em associação com corticoide com melhoria clínica. O diagnóstico adequado e a administração precoce de antibiótico foram os pontos-chave para o sucesso terapêutico, uma vez que esta patologia se associa a elevada taxa de mortalidade. Este diagnóstico não deverá ser esquecido.

Palavras-chave: Elevada imunossupressão; febre; insuficiência respiratória; pneumonia por *pneumocystis jiroveci*; transplante renal.

INTRODUCTION

Potential etiologies of infection in kidney transplant patients are diverse, ranging from common community acquired infectious diseases to uncommon opportunistic infections. The timetable of the infection etiology after transplantation is critical, different time points in the post-transplant period could be defined and each one carry higher risk for different forms of infection¹⁻³. *Pneumocystis jiroveci* is a well-known opportunistic fungus that can cause life-threatening pneumonia in kidney transplant patients mostly within the first 6 months post-transplantation⁴⁻⁷. In the absence of prophylaxis, *Pneumocystis jiroveci* pneumonia (PCP) occurs in 2%-4% of renal transplant patients, with a mortality rate of up 49%^{7,8}. Its incidence has decreased since the introduction of PCP prophylaxis^{9,10}. Trimethoprim-sulfamethoxazol (TMP-SMX) prophylaxis is recommended for 3-6 months after transplantation

and proved to be safe, effective and allowed reduction of the infection¹¹. This entity may occur after one year post transplant, but the rate is very low^{4,7,8}. High immunosuppression dose, cytomegalovirus infection, previous history of acute rejection and poor GFR are risk factors for the occurrence of PCP in kidney transplant patient^{7,9,12}. The onset of disease is usually insidious with dry cough and dyspnea; however in some cases the presentation can be subtle and non-specific¹³. Typical radiographic features are bilateral interstitial infiltrates. The treatment of choice is with high dose of TMP-SMX during 21 days, reduction in the immunosuppressive therapeutic and, in severe cases (defined by PaO₂ < 70 mmHg or an arterial-alveolar gradient > 35 mmHg), association with steroids¹¹. Early diagnosis and prompt administration of empiric antimicrobial therapeutic are the cornerstones of successful treatment since this disease is associated with high mortality rate.

■ CASE REPORT

A 51-year-old Caucasian male with a history of chronic renal failure secondary to a chronic glomerulonephritis received a second living kidney transplant (from his sister) in 2001. The patient had poor therapeutic compliance and had an episode in 2001 of cellular rejection treated with OKT3. He had chronic graft dysfunction with serum creatinine ranging from 2 to 2,5 mg/dl. His maintenance immunosuppressive treatment consisted of mycophenolate mofetil (MMF) 750 mg 2 times a day, cyclosporine (CsA) 75 mg plus 50 mg/day and prednisolone 7,5 mg/day (did not correspond to his doctor prescription). Other medication included antihypertensive agents, statin and aspirin. Four months prior to that admission he has been hospitalized for acute coronary syndrome and upper gastrointestinal bleeding (perforation of gastric ulcer). Antigenemia assay for cytomegalovirus (CMV) in that period was positive (27cells/50.000). Although remaining asymptomatic for CMV disease, he was treated with valgancyclovir during three weeks. In the last control CMV antigenemia was negative.

In the current episode the patient was admitted to the hospital with a 3-day history of asthenia, fever and genitourinary complains. On presentation, the patient appeared comfortable. He had a temperature of 38°C, pulse rate of 84/min, blood pressure of 104/65 mmHg (normal value), respiratory rate of 16/min and pulse oximetry of 100% in ambient air. Examination of the lungs, heart and abdomen revealed no abnormalities. The graft was painless. Laboratory tests revealed leukocytosis $12,13 \times 10^3$ /L (neutrophils 80,7%, lymphocytes 14,2%), normochromic-normocytic anemia (Hgb 10,9 g/dL); worse graft function (creatinine 3,25 mg/dl and urea 292 mg/dl); protein c reactive 55 mg/L; no change of hepatic function; urinary sediment with leukocytes. Chest x-ray was unremarkable and renal ultrasound showed no changes. Despite the initial treatment for presumed cystitis with amoxicillin and clavulanate the patient got worse. He maintained persistent high fever ($> 38,5^\circ\text{C}$) and developed dry cough, chills, hypoxemia, cyanosis and rapidly progressive dyspnea. Physical examination revealed signs of respiratory distress; tachycardia (HR – 130 bpm sinus rhythm); cyanosis; hypoxemia; crackles and wheezing on auscultation of thorax. Oxygen saturation dropped and arterial blood gas showed type 1 respiratory

failure (pH- 7,4, pO₂ – 51 mmHg, pCO₂ – 24 mmHg). Laboratory tests showed a worse graft function (Urea – 286 mg/dl, Creatinine – 4,61 mg/dL) and elevation of inflammatory parameters (protein c reactive – 374 mg/L, leucocytes – 17×10^3 /L). Antigenemia assay for CMV was positive 5/50000 and began oral valganciclovir 450 mg/day. Chest x – ray revealed diffuse bilateral infiltrates, suggestive of PCP. The patient progressively worsened and developed severe respiratory distress. On the 3th day of admission he was transferred to the intensive care unit and started non-invasive ventilation. Neither dialysis nor vasopressor support was necessary. A bronchoscopy was done and *Pneumocystis Jiroveci* was identified in the bronchoalveolar lavage fluid. Blood and urine cultures were persistently negatives. HIV serology was negative. The patient was given TMP-SMX 15 mg/kg for 21 days plus prednisolone (60 mg/day initially, then tapered), MMF was suspended. A good clinical improvement was observed 48 hours after. At the 12th day of hospitalization the patient was transferred back to the service of nephrology and restarted MMF. A good clinical evolution was observed having been discharged from the hospital at 22th day. Presently the patient is asymptomatic, recovered the baseline levels of creatinine and keeps prophylaxis for pneumocystis pneumonia.

■ DISCUSSION

Pneumocystis pneumonia is a feared and serious opportunistic infection in immunocompromised patients, including kidney transplant patients, associated with high morbidity and mortality^{6,11,12}. Defects in T lymphocyte than in B lymphocyte are important mechanisms in the pathogenesis of this entity^{4,14,15}.

The diagnosis of PCP relies on clinical suspicion with microbiological confirmation⁶. Approximately 5% of patients develop pneumocystis jiroveci pneumonia after renal transplantation if they do not receive prophylaxis¹⁶. According to KDIGO guidelines PCP prophylaxis must be done in all renal transplant recipients for 3-6 months after transplantation, however some experts recommend a more prolonged and perhaps even indefinite use of PCP prophylaxis, in selected cases^{11,12}. Nowadays biological therapies are increasing, which may cause prolonged immunosuppression and extended prophylaxis may be needed⁹.

In renal transplant recipients, PCP occurs during the early post-transplantation period because after that time most patients are receiving stable and relatively modest levels of immunosuppression. The incidence of PCP in moderately immunosuppressed renal transplant patients is as low as 0,6% but increases exponentially with additional immunosuppressive factors^{9,17}.

The type of immunosuppressive regimen used has influence in the incidence of PCP. In a study conducted in Germany between 1986 and 1994, more cases of PCP were observed with the use of tacrolimus, anti-thymocyte globulin (ATG) and corticosteroids than with the use of cyclosporine A¹⁸. According some reports the incidence of PCP were 3% in patients treated with azathioprine vs. 9% in those treated with CsA; others showed an incidence of 1% in patients treated with CsA vs. 14% in those receiving tacrolimus¹⁶. It was also demonstrated that sirolimus was associated with an increased risk of PCP¹⁶.

MMF in a rat model presented an anti-*Pneumocystis* activity through the inhibition of inosine monophosphate dehydrogenase (IMPDH)¹⁴. That inhibition depletes guanosine nucleotides resulting in a semi specific inhibition of T and B lymphocyte proliferation and antibody production¹⁴. However this protection has not been observed in humans¹⁸ and some studies recognize it as a risk factor for PCP^{12,15}. Potentially risk factors for the development of PCP are still poorly defined and some are controversial^{9,12}. However, higher maintenance levels of immunosuppressive therapy; some periods of intensified immunosuppression (due to high doses of corticosteroids, calcineurin inhibitors, antilymphocyte antibody or other T-cell-depleting therapies); number of rejection treatments (1 treatment – 2 fold increase, 3 treatments – 10 fold increase in PCP); periods of neutropenia; immunomodulating infections (tuberculosis, hepatitis C) and CMV infection are well known risk factors^{4,5,7,9,12,15,16,18}.

This late infection is associated with a non-specific immunosuppressive syndrome which can lead to superinfection with other opportunistic pathogens⁷. There are several studies that demonstrate that CMV infection was found to increase the risk PCP by itself. CMV infection alters host immune responses by a variety of mechanisms: suppression of helper

T-cell function and inhibitory effect on alveolar macrophages^{7,19}. A low eGFR might result in a prolonged renal clearance of immunosuppressants that induce more immunosuppression¹².

The number of T-helper cells may be a useful marker for estimating the risk of PCP in patients receiving immunosuppressive therapy²⁰. According some reports, a count of CD4+ lymphocyte below 200/microl is associated with an increased risk for this disease. More studies are needed, but CD4 count could be an important marker in the identification of patients who might benefit in the reinstitution or prolonging PCP prophylaxis.

The episode of PCP in our patient seemed to be related with a state of severe immunosuppression (high MMF dose, low eGFR, antigenemia for CMV positive).

This report describe a case of late PCP in a time that was unexpected, identified some risk factors for this entity and showed that this infection must be included in the differential diagnosis independently of post-transplant time. Strategies for prevention of PCP must be individualized and in some cases may be justifiable to restart or extended PCP prophylaxis besides three-six months after transplantation. Life-long secondary prophylaxis is suggested by some experts, however no recent data are available on how many recipients experience recurrence of PCP after a renal transplant. There are few data in identifying patients who could benefit from this therapeutic approach (secondary or extended PCP prophylaxis). According some surveys patients receiving – corticosteroids with 20 mg/day of prednisolone for a period of 2-3 weeks, therapy for CMV infection; those with – prolonged neutropenia, chronic graft dysfunction or higher levels of immunosuppression and patients who are treated for acute allograft rejection, PCP prophylaxis must be weighted⁴. In addition to the recommended systematic post-transplant prophylaxis (within 3-6 months after transplantation) patients who are treated for rejection any time should also be given TMP-SMX prophylaxis for 3-4 months period¹⁶. Secondary prophylaxis is also needed after treatment of PCP¹⁵ and in situations that are not possible to reduce immunosuppression therapy after an episode of *Pneumocystis* pneumonia, prophylaxis should be maintained indefinitely^{4,21}. In the other clinical

situations mentioned above the duration of prophylaxis is not well defined, however a period of 3-4 months should be thought.

Early diagnosis and prompt administration of empiric antimicrobial therapeutic are the cornerstones of successful treatment since this disease is associated with a mortality rate that may reach 50% in kidney transplant recipients²². Late presentation of PCP is rare^{4,7,8} however this diagnosis should never be forgotten.

In our case, the high clinical suspicion in association with an early institution of therapy was fundamental to a good outcome. The dose of immunosuppression was substantially reduced (on the date of hospital discharge) and it was opted to maintain (secondary prophylaxis) treatment for PCP for a minimum of 3 months.

In summary, although randomized trials are lacking, the recipient's risk should be assessed and those at high risk of infection prophylaxis must be offered regardless of the time after transplantation.

Conflict of interest statement: None declared.

References

1. Pizzo PA. Fever in immunocompromised patients. *N Engl J Med* 1999;341(12):893-900.
2. Fishman JA, Rubin RH. Infection in organ-transplant recipients. *N Engl J Med* 1998;338(24):1741-51.
3. Fishman JA. Infection in renal transplant recipients. *Semin Nephrol* 2007;27(4):445-61.
4. Fishman JA. Prevention of infection caused by *Pneumocystis carinii* in transplant recipients. *Clin Infect Dis* 2001;33(8):1397-405.
5. Radisic M, Lattes R, Chapman JF, del Carmen Rial M, Guardia O, Seu F, et al. Risk factors for *Pneumocystis carinii* pneumonia in kidney transplant recipients: a case-control study. *Transpl Infect Dis* 2003;5(2):84-93.
6. Charles F Tomas AHL. Epidemiology, clinical manifestations, and diagnosis of *Pneumocystis pneumonia* in non-HIV-infected patients. www.uptodate.com 2013.
7. Muhammad Iqbal AH, Lim SK, Ng KP, Tan LP, Chong YB, Keng TC. *Pneumocystis jirovecii* pneumonia 13 years post renal transplant following a recurrent cytomegalovirus infection. *Transpl Infect Dis* 2012;14(4):E23-6.

8. Gordon SM, LaRosa SP, Kalmadi S, Arroliga AC, Avery RK, Truesdell-LaRosa L, et al. Should prophylaxis for *Pneumocystis carinii* pneumonia in solid organ transplant recipients ever be discontinued? *Clin Infect Dis* 1999;28(2):240-6.
9. McCaughan JA, Courtney AE. *Pneumocystis jirovecii* pneumonia in renal transplantation: time to review our practice? *Nephrol Dial Transplant* 2012;27(1):13-5.
10. Green H, Paul M, Vidal L, Leibovici L. Prophylaxis for *Pneumocystis pneumonia* (PCP) in non-HIV immunocompromised patients. *Cochrane Database Syst Rev* 2007(3):CD005590.
11. KDIGO clinical practice guideline for the care of kidney transplant recipients. *Am J Transplant* 2009;9 Suppl 3:S1-155.
12. Struijk GH, Gijsen AF, Yong SL, Zwinderman AH, Geerlings SE, Lettinga KD, et al. Risk of *Pneumocystis jirovecii* pneumonia in patients long after renal transplantation. *Nephrol Dial Transplant* 2011;26(10):3391-8.
13. Thomas CF, Jr., Limper AH. *Pneumocystis pneumonia*: clinical presentation and diagnosis in patients with and without acquired immune deficiency syndrome. *Semin Respir Infect* 1998;13(4):289-95.
14. Oz HS, Hughes WT. Novel anti-*Pneumocystis carinii* effects of the immunosuppressant mycophenolate mofetil in contrast to provocative effects of tacrolimus, sirolimus, and dexamethasone. *J Infect Dis* 1997;175(4):901-4.
15. Goto N, Oka S. *Pneumocystis jirovecii* pneumonia in kidney transplantation. *Transpl Infect Dis* 2011;13(6):551-8.
16. European best practice guidelines for renal transplantation. Section IV: Long-term management of the transplant recipient. IV.7.1 Late infections. *Pneumocystis carinii pneumonia*. *Nephrol Dial Transplant* 2002;17 Suppl 4:36-9.
17. 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(3):421-3.
18. 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, table of contents.
19. Freeman RB, Jr. The 'indirect' effects of cytomegalovirus infection. *Am J Transplant* 2009;9(11):2453-8.
20. Gluck T, Geerdes-Fenge HF, Straub RH, Raffenberg M, Lang B, Lode H, et al. *Pneumocystis carinii* pneumonia as a complication of immunosuppressive therapy. *Infection* 2000;28(4):227-30.
21. Ito M, Nozu R, Kuramochi T, Eguchi N, Suzuki S, Hioki K, et al. Prophylactic effect of FK463, a novel antifungal lipopeptide, against *Pneumocystis carinii* infection in mice. *Antimicrob Agents Chemother* 2000;44(9):2259-62.
22. Fritzsche C, Riebold D, Fuehrer A, Mitzner A, Klammt S, Mueller-Hilke B, et al. *Pneumocystis jirovecii* colonization among renal transplant recipients. *Nephrology (Carlton)* 2013;18(5):382-7.

Correspondence to:

Dr^a Cláudia Bento

Department of Nephrology, Centro Hospitalar de Trás-os-Montes e Alto Douro. Avenida da Noruega, 5000-508 Lordele. Vila Real, Portugal