Pneumonia por *Pneumocystis jirovecii*: 14 Anos de Experiência num Serviço de Medicina Intensiva

Pneumocystis jirovecii Pneumonia: 14 Years of Experience in an Intensive Care Unit

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Resumo

Introdução: A pneumonia por *Pneumocystis jirovecii* (PJP) afecta indivíduos imunocomprometidos. É a infecção oportunista mais frequente em infectados com o vírus da imunodeficiência humana (VIH). Apesar de um declínio na sua incidência, a PJP grave continua a ser uma causa comum de admissão em serviços de Medicina Intensiva (SMI).

Material e Métodos: Estudo retrospectivo (2000-2013) dos doentes com PJP admitidos num SMI de um hospital universitário. Foram analisados os factores de risco, diagnóstico, tratamento, tempo de internamento e mortalidade.

Resultados: Identificados 27 doentes com idade média de 47,7 (±13, 4) anos; 81,7% do sexo masculino. Os factores de riscos identificados foram: infecção VIH (44,4%), transplante (18,5%), neoplasia (7,4%), vasculite e hepatite C (3,7%). Em 22,2% nenhum factor de risco foi identificado. Em 83,3% dos doentes VIH+, esse diagnóstico era desconhecido; nenhum estava sob profilaxia. Todos os pacientes VIH+ tinham CD4 + < 200 células/microL. O PJ foi identificado principalmente (96,3%) no lavado broncoalveolar. Foi necessária ventilação mecânica invasiva em 96,3% e vasopressores em 62,9%. Três doentes VIH+ mantiveram-se sob terapêutica antiretroviral durante o internamento. Sete (25,9%) desenvolveram pneumotórax. O tempo médio de internamento foi 17,4 dias. A mortalidade atingiu 51,9%.

Conclusão: A PJP atingiu sobretudo homens jovens com infecção VIH e CD4 + < 200 células/microL. Um número significativo não tinha factores de risco. Na maioria, o diagnóstico foi realizado no LBA. O cotrimoxazol foi sempre a primeira opção terapêutica. O número de indivíduos sob TAR foi baixo. A gravidade e a mortalidade dos doentes foram elevadas.

Palavras-chave: Cuidados Intensivos; Infecção por VIH; Pneumonia por Pneumocystis; Pneumocystis jiroveccii

Abstract

Background: *Pneumocystis jirovecii pneumonia (PJP) is a condition that affects immunocompromised individuals. It is the most common opportunistic infection in human immunodeficiency virus (HIV) infected individuals. Despite a decline in its incidence, severe PJP continues to be a common cause of intensive care unit (ICU) admission.*

Material and Methods: *Retrospective study (2000-2013) of patients with PJP admitted to an ICU at a university hospital. Data regarding risk factors, diagnosis, treatment, length of stay and mortality was analyzed.*

Results: *A total of 27 patients with a mean age of 47.7 (+13.4) years were identified, from which 81.7% were male. Identified risks factors were HIV infection (44.4%), transplant (18.5%), neoplasms (7.4%), vasculitis and hepatitis C (3.7%). No risk factor was identified for 22.2%. In 83.3% of the HIV patients, this diagnosis was unknown and none was on prophylaxis. All HIV patients had CD4+ < 200 cells/microL. PJ was mainly (96.3%) identified on bronchoalveolar lavage (BAL). Invasive mechanical ventilation and vasopressors were necessary for 6.3% and 62.9% of the patients, respectively. Three HIV positive patients stayed on ART during treatment. Seven patients (25.9%) developed pneumothorax. The mean length of hospital stay was 17.4 days. Mortality reached 51.9%.*

Conclusion: *PJP affected mainly young male individuals with HIV infection and CD4+ < 200 cells/µL. A significant number of patients had no identifiable risk factor for PJP. In most cases, the diagnosis was carried out in BAL. The co-trimoxazole was the first therapeutic option in all cases. The number of individuals under ART was low. Both severity and mortality of the patients were high.*

Keywords: Critical Care; HIV Infections; Pneumocystis jirovecii; Pneumonia, Pneumocystis

Introduction

Pneumocystis jirovecii (PJ) was first identified as a protozoan but since 1988 it was reclassified as a fungus.[1] It is the etiological agent of *Pneumocystis jirovecii* pneumonia (PJP), an acute and life threatening condition that affects immunocompromised individuals. This condition is the most frequent opportunistic infection in HIV infected individuals, especially in those with a CD4+ count < 200 cel/microL, and is an acquired immune deficiency syndrome (AIDS) defining disease.[2,3] Other patients are also vulnerable, such as those submitted to some kind of immunossupression (transplant, neoplasm, connective tissue disease, etc.).[3] However, PJP was described in patients with no known predisposing illness in few anecdoctal case reports.[4,5] Antiretroviral therapy (ART) in human immunodeficiency virus (HIV) patients has reduced its incidence in this population; however, as the use of immunossupressive medications is growing, incidence of PJP is increasing.[3]

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Tabela 1: Characterization of the population

		N	(%)
Gender	Male	22	81,7%
	Female	5	18,3%
Age (years)	Average ± SD	47,7 ± 13,4	
	Minimum - Maximum	20-74	
Risk Factors	HIV	12	44,4%
	Renal transplant	5	18,5%
	Neoplasm	2	7,4%
	Systemic vasculitis	1	3,7%
	Hepatitis C	1	3,7%
	None	6	22,2%

It may have an indolent course in HIV positive patients, presenting with unspecific symptoms such as subtle progressive dyspnea, non-productive cough and low grade fever.[2] In patients with other risk factors, it usually has a more abrupt presentation, with acute respiratory failure, frequently following immunossupressive medications.[6] Chest radiograph usually shows bilateral perihilar interstitial infiltrates that become increasingly homogeneous and diffuse as the disease progresses.[7] PJ does not grow in conventional culture media; the use of direct immunofluorescence antibody staining using a fluorescein conjugated monoclonal antibody to detect cysts and trophic forms in respiratory specimens, especially in bronchoalveolar lavage (BAL), is the gold standard for diagnosis.[8,9] Pneumothorax is a known complication of the disease.[10]

Treatment with trimethoprim–sulfamethoxazole is the most effective choice.[2,11] With the increasing incidence of the disease, concern has emerged regarding the possibility of resistance to conventional therapy.[2]

Respiratory failure is usually the reason for admission of patients with PJP in intensive care unit (ICU).[2] Mortality rates can reach 10-20% in HIV infected patients, but it can be higher if mechanical ventilation is needed.[9,12] Among HIV negative patients, it can reach 30-60%, with a greater risk of death among transplanted ones or those with connective-tissue disease.[3,13,14]

The purpose of this study was to characterize the demographic and the clinical features of the population of PJP patients admitted to the ICU of Coimbra's University Hospital with the diagnosis of PJP.

Material and Methods

A retrospective study of patients admitted to the multipurpose ICU at the 1300-bed Coimbra University Hospitals (Portugal) with the diagnosis of PJP from 2000 to 2013 was performed, by consulting patients' medical charts. Diagnosis of PJP was established in patients with respiratory complaints and bilateral infiltrates on chest radiograph in whom PJ was documented in respiratory specimens. Data regarding risk factors, diagnosis, treatment, length of stay and mortality was analyzed. Data are presented as mean and standard deviation (SD) or frequencies and percentages. Statistical analysis employed SPSS 19.0 (SPSS, Chicago, IL, USA).

Results

We found 31 patients with the diagnosis of PJP, but only 27 were included because we were unable to get the clinical records of the remaining. Most of the patients (n = 22; 81.7%) were male and the mean age was 47.7 years. (Table 1)

The most prevalent risk factor identified for acquiring such an infection was HIV infection (n = 12; 44.4%). Patients submitted to renal transplant were also affected and were responsible for 18.5% of the cases, corresponding to five patients. Other risk factors were identified, such as neoplasms, vasculitis on immunossupressive therapy and hepatitis C medicated with peginterferon. In 6 patients (22.2%) no risk factor was identified, despite exhaustive investigation. (Table 1)

When considering the twelve patients with HIV infection, in ten (83.3%) this diagnosis was unknown and made during their stay in the ICU. The remaining were on ART but none was on prophylaxis (Table 2). All HIV positive patients had CD4+ counts < 200 cells/microL. (Table 3)

Regarding the six patients with no identified risk factor, the mean age was 49,9 years and half were man. In five of them (83.3%) PJ was identified in BAL and on one it was isolated on endotracheal aspirate. Two patients had also a positive serology for *Chlamydia pneumoniae* and one had a positive urinary antigen for *Legionella pneumophila*. (Table 4)

Of the remaining patients, only 3 (20%) renal transplanted patients were on prophylaxis.

In 26 (96.3%) patients, diagnosis was obtained with positive imunoflorescence in bronchoalveolar lavage (BAL) and mini-BAL. On the remaining, PJ was identified on endotracheal aspirate.

Other microorganisms were concomitantly identified in patients with PJP, as previously mentioned. Two (7.4%) patients had a positive serology for *Chlamydia pneumoniae* and two (7.4%) had a positive serology for CMV. One (3.7%) patient had a positive sputum culture for *Aspergillus fumigatus* and one (3.7%) had a positive urinary antigen for *Legionella pneumophila*.

When considering the radiological pattern, in 55.6% (n = 15) a diffuse alveolar infiltrate was observed on chest x-ray. The remaining showed a diffuse interstitial infiltrate (37%; n = 10) or a lobar infiltrate (7.4%; n = 2)

Twenty-six patients (96.3%) required invasive mechanical ventilation and seventeen (62.9%) needed vasopressors.

Tabela 2: HIV positive patients´ characteristics

		N	(%)	N	(%)
Gender	Male	11	8.3		
	Female	1	91.7		
Age (years)	Average ± SD	43.9 ± 13.1			
	Minimum - Maximum	25-74			
Previous diagnosis	Yes	2	16.4	Prophylaxis 0	0
				ART*	100
	No	10	83.3		

* ART (antiretroviral therapy)

Tabela 3: CD4+ counts and viral load of HIV positive patients

	Mean	SD	Minimum	Maximum
CD4+ (cells/microL)	43.1	44.8	5.0	112
Viral Load (copies/mL)	455966.1	571217.2	75000	1797000

Trimethoprim-sulfamethoxazole was the initial therapy of choice in all patients. Due to adverse reactions, 3 (11.1%) patients had to be changed to atovaquone and one (3.7%) of them also needed to be later changed to clindamycin and primaquine due to gastrointestinal distress caused by atovaquone. Only 3 HIV positive patients (25%) started or stayed on ART during treatment for PJP. Seven patients (25.9%) developed pneumothorax.

Mean SAPS II was 40.5 (SD 11.5, min 22, max 52) and mean APACHE II score was 17.7 (SD 7.7, min 6, max 34).

The mean length of stay in the ICU was 17.4 days (SD 14.5, min 1, max 57). The mortality rate was 58.3% (n = 7) for HIV positive patients and 46.7% (n = 7) for the remaining. Overall mortality reached 51.9% (n = 14).

Discussion

Similarly to other series, PJP involved mainly male young individuals with HIV infection.[15] Unusual and surprising was the number of patients who had no identifiable risk factor for infection by *P. jirovecii*. The authors are not aware of a series with similar results.[15,16] This finding had already been described in sporadic cases and no explanation is presently known.[4,5] The fact that two of them had positive serologic tests for Chlamydia and one of them for Legionnella could raise the question of the importance of PJ as the etiologic agent but does not explain occurrence of PJP in the remaining three. If this is to be confirmed in similar studies, the consideration of PJ as the etiological agent of pneumonia in patients with no risk factors should gain awareness.

The amount of new diagnosis of HIV was high (83.3%) when compared to other studies (23-58.7).[17,18] The suspicion in these circumstances can be diminished and so a careful medical history and the radiological characteristics are important clues to suspect of PJ in patients not previously diagnosed.

Few patients were on a prophylactic regimen for PJ. Considering that all HIV patients had CD4+ counts < 200 cells/microL and two of them had been previously diagnosed, prophylaxis was recommended. This situation should be revised as it benefits are well established.[11,19-21]

In most cases, the diagnosis was carried out at the BAL and mini-BAL; however PJ was also isolated on endotracheal aspirate and this should encourage clinicians to search for PJ in other specimens rather than BAL which requires more invasive technics.[22,24]

The co-trimoxazole was the first therapeutic option in all cases as recommended for both HIV positive and negative patients.[2,11] The number of individuals under ART during hospitalization was low and concerning recent data on the benefits of early institution of ART in these patients, future practices are to be revised.[25,26]

Our data showed a high mortality compared to other studies that can be at least partially explained by the high severity of the disease in these patients.[16] Most of the patients required mechanical ventilation and a high number needed vasoactive drugs and developed pneumothorax, factors associated with higher mortality in previous studies.[15,27] The amount of patients requiring mechanical ventilation and vasopressors was higher when compared to other series that had lower mortality rate.[15] The low institution of ART during hospitalization among HIV patients, that can reduce mortality by almost half, can be another explanation and reinforces the need to always consider early ART.[26]

Mortality was higher in HIV patients, contrarily to other series.14,28 The mortality rate and the length of stay of PJP patients are also higher when compared with the mean values of these variables for this ward during this period of time (25-30% and 10-11 days, respectively).

Tabela 4: No-risk factor patients' characteristics

		N	(%)
Gender	Male	3	50%
	Female	3	50%
Age (years)	Average ± SD	49.9 ± 13.1	
	Minimum - Maximum	36-68	
Other microorganims	Chlamydia pneumoniae	2	33%
Diagnosis	Legionella pnemophila	1	16.7%
	BAL*	5	83.3%
	Endotracheal aspirate	1	16.7%

* Bronchoalveolar lavage

Conclusion

PJP involved mainly male young individuals with HIV infection and CD4+ values <200 cells/microL. A significant number of patients had no identifiable risk factor for infection by *P. jirovecii*, a finding that deserves attention. Most of the patients had not been previously diagnosed, and so HIV should always be suspected, especially in young patients with no risk factors for pneumonia. In most cases, the diagnosis was carried out in the BAL and mini-BAL. The co-trimoxazole was the first therapeutic option in all cases. The number of individuals under ART during hospitalization was low, a factor that requires attention. The severity of the patients was considerable and mortality high. ■

Protecção de Seres Humanos e Animais: Os autores declaram que não foram realizadas experiências em seres humanos ou animais.

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Referências

1. Edman JC, Kovacs JA, Masur H, Santi DV, Elwood HJ, Sogin ML. Ribosomal RNA sequence shows Pneumocystis carinii to be a member of the fungi. Nature. 1988;334:519-22.
2. Thomas CF, Jr., Limper AH. Pneumocystis pneumonia. New Engl J Med.2004;350:2487-98.
3. Sepkowitz KA. Opportunistic infections in patients with and patients without Acquired Immunodeficiency Syndrome. Clin Infect Dis. 2002;34:1098-107.
4. Jacobs JL, Libby DM, Winters RA, Gelmont DM, Fried ED, Hartman BJ, et al. A cluster of Pneumocystis carinii pneumonia in adults without predisposing illnesses. New Engl J Med. 1991;324:246-50.
5. Cano S, Capote F, Pereira A, Calderon E, Castillo J. Pneumocystis carinii pneumonia in patients without predisposing illnesses. Acute episode and follow-up of five cases. Chest. 1993;104:376-81.
6. Yale SH, Limper AH. Pneumocystis carinii pneumonia in patients without acquired immunodeficiency syndrome: associated illness and prior corticosteroid therapy. Mayo Clin Proc. 1996;71:5-13.
7. DeLorenzo LJ, Huang CT, Maguire GP, Stone DJ. Roentgenographic patterns of Pneumocystis carinii pneumonia in 104 patients with AIDS. Chest. 1987;91:323-7.
8. Catherinot E, Lanternier F, Bougnoux ME, Lecuit M, Couderc LJ, Lortholary O. Pneumocystis jirovecii Pneumonia. Infect Dis Clin North Am. 2010;24:107-38.
9. Miller RF, Huang L, Walzer PD. Pneumocystis pneumonia associated with human immunodeficiency virus. Clin Infect Dis. 2013;34:229-41.
10. Murry CE, Schmidt RA. Tissue invasion by Pneumocystis carinii: a possible cause of cavitary pneumonia and pneumothorax. Hum Pathol. 1992;23:1380-7.
11. Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America.[accessed Dec 2015] Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf.
12. 12. Curtis JR, Yarnold PR, Schwartz DN, Weinstein RA, Bennett CL. Improvements in outcomes of acute respiratory failure for patients with human immunodeficiency virus-related Pneumocystis carinii pneumonia. AmJ Respir Crit Care Med. 2000;162:393-8.
13. Pareja JG, Garland R, Koziel H. Use of adjunctive corticosteroids in severe adult non-HIV Pneumocystis carinii pneumonia. Chest. 1998;113:1215-24.
14. Roembke F, Heinzow HS, Gosseling T, et al. Clinical outcome and predictors of survival in patients with pneumocystis jirovecii pneumonia-results of a tertiary referral centre. Clin Respir J. 2014;8:86-92.
15. 15. Solano LM, Alvarez Lerma F, Grau S, Segura C, Aguilar A. Neumonia por Pneumocystis jiroveci: caracteristicas clinicas y factores de riesgo asociados a mortalidad en una Unidad de Cuidados Intensivos. Med Intensiva. 2015;39:13-9.
16. Klofteridis DP, Valachis A, Velegraki M, Antoniou M, Christofaki M, Vrentzos GE, et al. Predisposing factors, clinical characteristics and outcome of Pneumonocystis jirovecii in HIV-negative patients. Kansenshogaku Zasshi. 2014;88:21-5.
17. Monnet X, Vidal-Petiot E, Osman D, Hamzaoui O, Hamzaoui O, Durrbach A, Goujard C, et al. Critical care management and outcome of severe Pneumocystis pneumonia in patients with and without HIV infection. Crit Care. Cr2008;12; R28.
18. Fei M, Sant C, Kim E, Swartzman A, Davis JL, Jarlsberg LG, et al. Severity and outcomes of Pneumocystis pneumonia in patients newly diagnosed with HIV infection: an observational cohort study. Scand J Infect Dis 2009;41:672-8.
19. Tomblyn M, Chiller T, Einsele H, Gress R, Sepkowitz K, Storek J, et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. Biol Blood Marrow Transplant. 2009;15:1143-238.
20. Martin SI, Fishman JA, Practice ASTIDCo. Pneumocystis pneumonia in solid organ transplantation. Am J Transplant.2013;13 Suppl 4:272-9.
21. Suryaprasad A, Stone JH. When is it safe to stop Pneumocystis jiroveci pneumonia prophylaxis? Insights from three cases complicating autoimmune diseases Arthritis Rheum. 2008;59:1034-9.
22. Zaman M, Wooten O, Suprahmanya B, Ankobiah W, Finch P, Kamholz S. Rapid noninvasive diagnosis of Pneumocystis carinii from induced liquefied sputum. Ann Intern Med.1988;109:7.
23. Cruciani M, Marcati P, Malena M, Bosco O, Serpelloni G, Mengoli C. Meta-analysis of diagnostic procedures for Pneumocystis carinii pneumonia in HIV-1-infected patients. Eur Respir J. 2002;20:982.
24. Willocks L, Burns S, Cossar R, Brettle R. Diagnosis of Pneumocystis carinii pneumonia in a population of HIV-positive drug users, with particular reference to sputum induction and fluorescent antibody techniques. J Infect. 1993;26:257.
25. Sarkar P, Rasheed HF. Clinical review: Respiratory failure in HIV-infected patients--a changing picture. Crit Care 2013;17:228.
26. Zolopa A, Andersen J, Powderly W, Sanchez A, Sanne I, Suckow C, et al. Early antiretroviral therapy reduces AIDS progression/death in individuals with acute opportunistic infections: a multicenter randomized strategy trial. PloS One 2009;4:e5575.
27. Miller RF, Allen E, Copas A, Singer M, Edwards SG. Improved survival for HIV infected patients with severe Pneumocystis jirovecii pneumonia is independent of highly active antiretroviral therapy. Thorax. 2006;61:716-21.
28. Monnet X, Vidal-Petiot E, Osman D, Hamzaoui O, Durrbach A, Goujard C, et al. Critical care management and outcome of severe Pneumocystis pneumonia in patients with and without HIV infection. Crit Care. 2008;12:R28.