"Pneumocystis carinii" pneumonia in patients with and without AIDS: a reappraisal

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Purpose: *Pneumocystis carinii* pneumonia (PCP), the most common life-threatening opportunistic infection in AIDS, has long been associated with other immunodeficiency states as well. Earlier reports suggested that the presentation of PCP in AIDS differed from that in other conditions, but both AIDS-related PCP and non-AIDS immunosuppressed states have evolved in recent years. In addition, if different patterns do exist, the presentation of PCP in AIDS is now much more likely to be familiar to physicians than non-AIDS PCP. This study was undertaken to compare the current clinical features of PCP in AIDS with those associated with other disorders. **Methods:** Retrospective review of medical records of all patients at our institution with confirmed PCP and AIDS during 1994 (17 patients) and without AIDS in the period of 1992-1994 (10 patients). **Results:** At presentation patients without AIDS had a significantly shorter duration of symptoms (8.4 ± 7.7 vs. 19.5 ± 10.2 days, $p < 0.05$), lower mean PaO_2 on room air (47 ± 8.2 vs. 63 ± 10 mm Hg, $p < 0.05$), and more frequent unilateral infiltrates on chest X ray (60 vs. 6%, $p < 0.05$). Importantly, the mortality rate for PCP was markedly higher in the non-AIDS group than in individuals with AIDS (40% vs. 6%, $p < 0.05$), and this was associated with delayed initiation of treatment in non-AIDS patients. **Conclusions:** Because of its acute course, atypical radiological presentation and high mortality, we conclude that the diagnosis of PCP should be persued early in the clinical course of patients receiving immunosuppressive therapy, and that prophylaxis should be strongly considered in individuals who will be immunosuppressed. *(J Pneumol 1997;23(2):79-82)*

Pneumonia por "Pneumocystis carinii" em pacientes com e sem SIDA: reavaliação

A pneumonia por Pneumocystis carinii *(PPC), que é a infecção oportunista que mais comumente põe em risco a vida de pacientes com síndrome da imunodeficiência adquirida (SIDA), tem sido há bastante tempo associada a outros estados de imunodeficiência. Os relatos iniciais sugeriram que a apresentação clínica da PPC em SIDA difere de sua apresentação em outras situações, embora ambas tenham sofrido modificações nos últimos anos. O objetivo do presente estudo é comparar os achados clínicos e laboratoriais da PPC em SIDA com os de pacientes portadores de PPC sem SIDA. Foram revisados os prontuários médicos de todos os pacientes em nossa instituição que tiveram o diagnóstico confirmado de PPC e SIDA durante o ano de 1994 (17 pacientes) e sem SIDA no período de 1992-1994 (dez pacientes). Quando da apresentação, os pacientes sem SIDA tinham uma duração de sintomas significativamente menor (8,4 ± 7,7* vs *19,5 ± 10,2 dias, $p < 0,05$), menor PaO_2 média a ar ambiente (47 ± 8,2* vs *63 ± 10mmHg, $p < 0,05$), e mais freqüente infiltrado unilateral no radiograma do tórax (60* vs *6%, $p < 0,05$). O índice de mortalidade da PPC foi marcadamente maior nos pacientes sem SIDA (40* vs *6%, $p < 0,05$), e este fato estava associado com retarde no início do tratamento específico nestes pacientes. Devido a seu curso mais agudo, apresentação radiológica atípica e alto índice de mortalidade, concluímos que o diagnóstico de PPC deve ser afastado em pacientes que recebem terapia imunossupressora e que profilaxia anti-PPC deve ser fortemente considerada em pacientes que serão imunossuprimidos.*

Key words – PCP-AIDS. PCP non-AIDS.

Descritores – PPC-AIDS. PPC não-AIDS.

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INTRODUCTION

The last 15 years have seen an explosive increase in the incidence of *Pneumocystis carinii* pneumonia (PCP), and in 1992 the Centers for Disease Control reported about 30,000 cases of PCP, making it one of the most common pulmonary infections in the USA[1]. The major factor behind this growth has been the dramatic spread of AIDS, and PCP initially was the index opportunistic infection in 64% of AIDS diagnoses

and occurred at least once in 80% of all cases[2]. As a result of recent advances, however, PCP now accounts for about 42% of all index diagnoses[1] and has in incidence in AIDS of 12.8 to 47.4 per 100 person-year depending on antiretroviral and chemoprophylaxis treatment[3]. In addition, the clinical features of PCP in AIDS have also evolved over the past decade, as extended survival and the use of prophylaxis have altered its presentation[4,5].

Among individuals with other immunosuppressive disorders, however, PCP is a problem that is increasing as well[6,7]. Before AIDS, PCP was an uncommon disease in the USA associated with immunosuppressive therapy and congenital immunodeficiencies. Only 194 cases were reported from 1967 to 1970[8] and an increasing but still modest number identified from 1973 through 1980[9,10]. Over the past decade or so, however, the incidence of PCP in these patients has risen dramatically as the types of illness treated with immunosuppressive therapy have broadened, more potent immunosuppressive agents have come into use, and improved supportive care has allowed for extended survival[7,11].

Therefore, because of the changes that have taken place with respect to AIDS-related and AIDS-independent *Pneumocystis carinii* infection, we undertook an analysis of the clinical features of PCP as it presents currently in these two groups of patients. Furthermore, since PCP associated with AIDS is now far more likely to be familiar to physicians than PCP in other immunosuppressed states, and now represents the "typical" pattern, we sought to identify features of PCP in non-AIDS patients that might contribute to less ready recognition in this group.

Methods

We retrospectively reviewed the records of all patients admitted to our institution without AIDS during the years 1992-1994, and with AIDS during 1994, who had PCP confirmed by histopathologic or cytologic examination of respiratory specimens. Patients were designated as having an immunodeficiency disorder other than AIDS if they had neoplastic or collagen vascular disease or had undergone organ transplant, and were receiving immunosuppressive or cytotoxic treatment. The clinical data were recorded at the time of presentation. Statistical analysis was performed using the Student's test and the Fisher exact test; $p < 0.05$ was considered significant.

Results

We identified 17 HIV-infected patients with PCP that was confirmed by sputum and/or bronchoscopic examination who were admitted to the hospital during 1994, including 13 men and 4 women with a mean age of 36.5 ± 5.4 years (table 1). During 1992-1994 there were 10 confirmed diagnosis of PCP in patients with immunodeficiencies other than AIDS. The underlying diseases included four patient with malignancies (two with Hodgkin's disease, and one each with multiple myeloma and chronic lymphocytic leukemia), one with severe rheumatoid arthritis, and five with organ transplants (one cardiac and two each with liver and renal transplants). This group is composed of 6 women and 4 men with a mean age of 50.2 ± 16.4 years, and all were receiving immunosuppressive and/or cytotoxic drugs. None of the non-AIDS group were receiving anti-*Pneumocystis carinii* prophylaxis while 4 patients in the AIDS group had been prescribed prophylaxis, but because compliance could not be determined it was uncertain if these cases represented failure of prophylaxis or lack of compliance.

Table 1 shows the clinical and laboratory data for each group. The duration of symptoms prior to presentation was significantly longer in the AIDS group than in the non-AIDS patients (19.5 ± 10.2 vs. 8.4 ± 7.7 days, respectively, $p < 0.05$). While a somewhat higher proportion of patients with AIDS reported sputum production (53 vs. 20%), this did not reach statistical significance, and there were no differences between the two groups in the frequency of any other symptom. In contrast, the chest X ray pattern at presentation differed in that 94% of the AIDS group had bilateral infiltrates while 60% of the non-AIDS group had unilateral lesions ($p < 0.05$). In addition, the non-AIDS group was significantly more hypoxemic at presentation than the AIDS group (PaO_2 on room air of 47 ± 8.2 vs. 63 ± 10 mm Hg; $p < 0.05$). Other laboratory features did not differ between the two groups.

TABLE 1
Clinical and laboratory data at presentation in AIDS and non-AIDS patients with PCP

	AIDS	Non-AIDS
Number	17	10
Sex (m:f)	13:4	4:6
Age (years)	35.6 ± 5.4	50.2 ± 16.4*
Symptoms		
Duration (days)	19.5 ± 10.2	8.4 ± 7.7*
Dyspnea	16 (94%)	9 (90%)
Cough	16 (94%)	8 (80%)
Fever	14 (82%)	7 (70%)
Sputum	9 (53%)	2 (20%)
Chest pain	4 (24%)	2 (20%)
Chest X ray infiltrates		
Bilateral	16 (94%)	4 (40%)
Unilateral	1 (6%)	6 (60%)
Laboratory		
PaO_2 (mm Hg on room air)	63 ± 10	47 ± 8.2*
Hematocrit (%)	33.2 ± 6.9	30.5 ± 4.5
Leukocytes (cells/mm^3)	5700 ± 2900	7100 ± 4600
Neutrophils (cells/mm^3)	4525 ± 2437	6175 ± 3992
Lymphocytes (cells/mm^3)	867 ± 648	609 ± 632
Albumin (g/dL)	3.1 ± 0.7	2.8 ± 0.7
LDH (U/L)	696 ± 410	998 ± 863

Values expressed as number and percentage (%) of patients or as mean ± SD; * $p < 0.05$.

A striking contrast was seen in mortality between the two groups ($p < 0.05$; table 2). One out of 17 patients with AIDS died (6%), while 4 of 10 without AIDS died (40%). To determine whether a delay in diagnosis and/or initiation of treatment may have contributed to the difference in mortality, we determined the time from presentation to beginning anti-PCP therapy (table 2). All patients with AIDS were started on effective anti-*Pneumocystis* treatment within the first 24 hours after presentation, likely reflecting the high level of suspicion for PCP. However, in most of the non-AIDS patients the anti-PCP treatment was started some days after presentation. Three patients in this group did not receive effective treatment until 5 or more days after presentation and one did nor receive specific treatment at all; 3 of these 4 patients died.

TABLE 2
Association between mortality and time from presentation to initiation of treatment

Patients	Time[a] (days)	Number of patients	Deaths (n)	Mortality (%)
AIDS	< 1	17	1	
AIDS total		17	1	6%
Non-AIDS	< 1	4	1	
	2	2	0	
	5	1	1	
	8	1	0	
	12	1	1	
	No treatment[b]	1	1	
non-AIDS total		10	4	40%*

a Time from initial presentation with respiratory symptoms to beginning anti-PCP therapy.
b Diagnosis at autopsy.
* $p < 0.05$ AIDS vs. non-AIDS.

Discussion

In this study we found that *Pneumocystis carinii* caused significantly different patterns of illness in HIV-infected individuals as compared with patients whose immunodeficiency resulted from other causes. Of note were the shorter duration of symptoms, greater proportion of atypical chest X ray patterns, and worse oxygenation at presentation. Most important, however, was a markedly higher mortality among non-AIDS patients. As a result, even though approximately 5 times as many cases of PCP were documented at our institution on an annualized basis among HIV-infected persons than in people with other immunodeficiencies, the number of PCP-related deaths in the two groups were roughly equivalent.

Our results are consistent in several aspects with a study undertaken early in the AIDS epidemic that compared AIDS and non-AIDS PCP[12]. Like that report, we found that patients with AIDS had a longer duration of symptoms and higher PaO_2 at presentation. In contrast, however, they reported that unilateral disease was similarly uncommon in both groups (5 and 2%, respectively), but we found that non-AIDS patients had a much higher incidence of "atypical" unilateral disease than AIDS patients (60 vs. 6%, respectively). Most strikingly, we found that PCP in AIDS had a much better survival than in other immunodeficiency states, while the earlier report found similar survival data. This difference is largely accounted for by a lower mortality among our AIDS patients (6%), since our non-AIDS PCP mortality (40%) was similar to the earlier study's mortality among both non-AIDS and AIDS patients (57 and 50%, respectively).

The reasons for this higher mortality in non-AIDS patients is likely multifactorial. While patients in the two groups cannot be compared directly, one possible explanation is that progress in the management of PCP in AIDS, such as improved recognition, diagnosis or treatment options, have not translated to the non-AIDS group. The shorter duration of symtoms prior to presentation and lower PaO_2 suggests that it progresses more rapidly and more severe disease in this group of patients but the reasons behind the more severe nature of disease in non-AIDS patients is unclear. Paradoxically, studies comparing the burden of organisms have shown that individuals with AIDS carry a substantially higher load of organisms[13,14], suggesting that simply the level of infection does not explain the more malignant course in non-AIDS PCP. Local immune responses have been postulated to play a critical role pathogenesis, and it is thus possible that different immune responses in the groups underlay the tendency to more severe disease. For example, bronchoalveolar neutrophils are higher in non-AIDS than AIDS-related PCP, and higher neutrophils numbers were found to correlate with poorer outcome[13]. In addition, the nature of underlying diseases resulting in immunosupression may contribute to differences in mortality. Similarly, the non-AIDS group was significantly older and may have included more individuals with co-morbid organ system disease.

Out data, however, suggest that a critical factor in the higher mortality among non-AIDS patients is a delay in treatment resulting from delayed recognition. While this is likely related to the multitude of diagnostic possibilities among non-AIDS immunocompromised patients with pulmonary infiltrates as contrasted with the predominance of PCP in AIDS, we believe that it may in part result from the atypical clinical presentation and chest X ray patterns.

While similarities and differences between PCP in AIDS and non-AIDS patients have been examined previously, this current re-assessment is needed for several reasons. Significant changes have occurred in the presentation and management of PCP in AIDS over the past number of years, including widespread prophylaxis, more efficient approaches to diagnosis such as non-invasive sputum examination, and the use of new drugs and adjunctive corticosteroids[3-5,15]. Similarly, non-AIDS patients at risk for PCP have evolved also as the number and types of disorders associated with immunodeficiency

states expanded, including more frequent organ transplants and more aggressive chemotherapy for malignancy and autoimmune diseases[16-27].

Critically important, however, is the fact that PCP as it presents in AIDS is now far more familiar to most physicians due to dramatic increase in AIDS-related PCP. This study demonstrates that PCP in non-AIDS-related conditions presents differently from the subacute process more typical in AIDS, with a more severe course and frequent atypical chest X ray patterns. Combined with its high mortality rate in non-AIDS patients, this argues for increased vigilance in order to ensure prompt recognition and early diagnosis and treatment.

REFERENCES

1. Centers for Disease Control and Prevention. HIV/AIDS surveillance report, year end edition. MMWR 1993;35:1-23.
2. Murray JF, Garay SM, Hopewell PC, Mills J, Snider GL, Stover DE. Pulmonary complications of the acquired immunodeficiency syndrome: an update (NHLBI workshop summary). Am Rev Respir Dis 1987;135: 504-509.
3. Bacellar H, Munoz A, Hoover DR, et al. Incidence of clinical AIDS conditions in a cohort of homosexual men with CD4+cell counts<100/mm^3. J Infect Dis 1994;170:1284-1287.
4. Wall PG, Porter K, Noone A, Goldberg DJ. Changing incidence of *Pneumocystis carinii* pneumonia as initial AIDS defining disease in the United Kingdom. AIDS 1993;7:1523-1525.
5. Soni P, Dinan W, Ravichandra P, Klapholz A, Talavera W. Clinical presentation of *Pneumocystis carinii* pneumonia with or without prophylaxis. Chest 1995;108:179S.
6. Sepkowitz KA. *Pneumocystis carinii* pneumonia in patients with AIDS. Clin Infect Dis 1993;17(Suppl 2):S416-S422.
7. Sepkowitz KA, Brown AE, Armstrong D. Editorial – *Pneumocysis carinii* pneumonia without acquired immunodeficiency syndrome – More patients, same risk. Arch Intern Med 1995;155:1125-1128.
8. Walzer PD, Perl DP, Krogstad DJ, Rawson PG, Schultz MG. *Pneumocystis carinii* pneumonia in the United States – Epidemiologic, diagnostic, and clinical features. Ann Intern Med 1974;80:83-93.
9. Burke BA, Good RA. *Pneumocystis carinii* pneumonia infection. Medicine (Baltimore) 1973;53:23-51.
10. Hughes WT. *Pneumocystis carinii* infection: an update. Medicine (Baltimore) 1992;71:175-178.
11. Varthalitis I, Meunier F. *Pneumocystis carinii* pneumonia in cancer patients. Can Treat Rev 1993;19:387-413.
12. Kovacs JA, Hiemenz JW, Macher AM, et al. *Pneumocystis carinii* pneumonia: a comparison between patients with acquired immunodeficiency syndrome and patients with other immunodeficiencies. Ann Intern Med 1984;100:663-671.
13. Limper AH, Offord KP, Smith TF, Martin II WJ. *Pneumocystis carinii* pneumonia – Differences in lung parasite number and inflammation in patients with and without AIDS. Am Rev Respir Dis 1989;140:1204-1209.
14. Ziefer A, Abramowitz JA. *Pneumocystis carinii* pneumonia in HIV positive and HIV-negative patients – An epidemiological, clinical and histopathological study of 18 patients. South Afr Med J 1989;76:308-313.
15. Hoover DR, Saah AJ, Bacellar H, et al. Clinical manifestations of AIDS in the era of pneumocystis prophylaxis. N Engl J Med 1993;329:1922-1926.
16. Kusne S, Dummer JS, Singh N, et al. Infections after liver transplantation: an analysis of 101 consecutive cases. Medicine (Baltimore) 1988; 67:132-143.
17. Mckenzie RS, Glenn LD, Goldsmith JC. *Pneumocystis carinii* pneumonia complicating multiple myeloma. Chest 1991;99:656-659.
18. Flood DA, Chan CK, Prunzanski W. *Pneumocystis carinii* pneumonia associated with methotrexate therapy in rheumatoid arthritis. J Rheumatol 1991;18:1254-1256.
19. Sepkowitz KA, Brown AE, Telzak EE, Gottlieb S, Armstrong D. *Pneumocystis carinii* pneumonia among patients without AIDS at a cancer hospital. JAMA 1992;267:832-836.
20. Berstein CN, Kolodny M, Block E, Shanahan F. *Pneumocystis carinii* pneumonia in patients with ulcerative colitis treated with corticosteroides. Am J Gastroenterol 1993;88:574-577.
21. Varthalitis I, Aoun M, Daneau D, Meunier F. *Pneumocystis carinii* pneumonia in patients with cancer. Cancer 1993;71:481-485.
22. Olsen SL, Renlund DG, O'Connel JB, et al. Prevention of *Pneumocystis carinii* pneumonia in cardiac transplant recipients by trimethoprim-sulfamethoxazole. Trends Biochem Sci 1993;56:359-362.
23. Slivka A, Wen PY, Shea WM, Loeffle JS. *Pneumocystis carinii* pneumonia during steroid taper in patients with primary brain tumors. Am J Med 1993;94:216-219.
24. Godeau B, Coutant-Perrone V, Huong DLT. *Pneumocystis carinii* pneumonia in the course of connective tissue disease: report of 34 cases. J Rheumatol 1994;21:246-251.
25. Ognibene FP, Shelhamer JH, Hoffman GS, et al. *Pneumocystis carinii* pneumonia: a major complication of immunosuppressive therapy in patients with Wegener's granulomatosis. Am J Respir Crit Care Dis 1995; 151:795-799.
26. Huynh-Do U, Gantenbein H, Binswanger U. *Pneumocystis carinii* pneumonia during immunosuppressive therapy for antineutrophil cytoplasmic autoantibody-positive vasculitis. Arch Intern Med 1995;155:872-874.
27. Gerrard JG. *Pneumocystis carinii* pneumonia in HIV-negative immunocompromised adults. Med J Aust 1995;162:233-235.