
The Frequency of *Pneumocystis carinii* in Patients with Haematologic Malignancies and Pneumonia

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ABSTRACT

Pneumocystis carinii (*P. carinii*) is an organism which was previously considered as a protozoan but recently it was shown to be more related to fungi. *P. carinii* increasingly causes opportunistic infections in immunocompromised patients. In this study, we detected *P. carinii* oocysts by indirect immunofluorescence test in 33 specimens obtained from 31 patients with haematological malignancies who had symptoms of pneumonia and investigated probable risk factors (corticosteroid usage, neutropenia duration, severe or mild neutropenia and type of haematological malignancy) for *P. carinii* pneumonia in *P. carinii* (+) patients. Although not statistically significant, PCP incidence was higher in relapsed acute leukemia (AL) patients (62.5%), patients with prolonged neutropenia (57.1%), and who received high dose ARA-C therapy (62.5%). *P. carinii* (+) patients were treated with trimethoprim-sulfamethoxazole. Six patients with PCP did not respond to therapy and died (50%). In conclusion PCP is not infrequent in AL (especially relapsed AL) and, indirectly we can suggest that chemoprophylaxis may be considered for these patients when they were in severe and prolonged neutropenia after high dose ARA-C therapy.

Key Words: *Pneumocystis carinii*, Acute leukemia, Non-Hodgkin's lymphoma, Multiple myeloma.

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INTRODUCTION

Pneumocystis carinii (*P. carinii*) is an organism which was previously considered as a protozoan but recently RNA and DNA studies showed that it is more related to fungi^[1]. *P. carinii* causes opportunistic infections in immunocompromised patients^[2]. Reactivation of cysts is the main cause of infection but, person-to-person or airborne transmission may also be possible^[3,4]. The presenting symptoms in most of the patients include dyspnea, fever, and cough and arterial blood gases reveal hypoxemia. Chest X-ray mostly shows diffuse interstitial pulmonary infiltrates but there may not be any finding also especially in neutropenic patients. The aim of this study was to evaluate the frequency of *P. carinii* infection in patients with haematological malignancies and symptoms of pneumonia at the same time in our unit and to detect any possible risk factors.

MATERIALS and METHODS

We investigated *P. carinii* oocysts in 33 specimens [16 sputum (without induction) and 13 bronchial lavage fluids, three pleural fluids and one open lung biopsy] obtained from 31 patients hospitalized between June 1998 and December 1999. Twenty-three patients were females and 8 were males. The median age was 45 years (range: 16-72 years). All of the patients had symptoms of pneumonia (fever, dyspnea, coughing with or without

sputum) and/or various pulmonary infiltrates on their chest X-ray. Specimens were obtained immediately after the appearance of symptoms of pneumonia, if the patient didn't able to produce sputum bronchial lavage fluids were obtained. None of the patients were receiving antibiotic against *P. carinii*.

Neutrophil counts below 500/mm³ were considered severe neutropenia, 500-1000/mm³ moderate, if higher than 1000/mm³ were considered mild neutropenia. If the duration of neutropenia (< 1500/mm³) was longer than 3 weeks it was accepted as prolonged neutropenia.

The patients characteristics according to diseases, neutrophil counts, high dose ARA-C treatment and corticosteroid usage were given in Table 1.

Eight of 16 patients with acute leukemia (AL) had de novo AL, rest of them were relapsed AL. Just at the time specimens were collected, two patients with de novo AL had received induction therapy with standard dose Ara-C and daunorubicin, three patients had consolidation therapy with high dose ARA-C (HD ARA-C 3 g/m² two times daily for 3 days) after standard dose induction therapy, and one patient died before chemotherapy. Five of the 8 relapsed AL patients had received HD ARA-C with daunorubicin and, two of them received fludarabine with ARA-C as induction therapy.

Table 1. The patients characteristics according to diseases, neutrophil counts, high dose ARA-C treatment and corticosteroid usage

	AL	NHL	MM	N
N	16	8	7	31
HD-ARA-C	8	-	-	8
Severe neutropenia	13	-	-	13
Mild-moderate neutropenia	1	1	7	9
Normal neutrophil counts	1	7	-	8
Prolonged neutropenia	4	-	3	7
Corticosteroid usage	0	5	7	12
Pretreatment	1	2	-	3

AL: Acute leukemia, NHL: Non-Hodgkin's lymphoma, MM: Multiple myeloma, HD-ARA-C: High dose cytosine arabinoside.

All of the 7 multiple myeloma (MM) patients were receiving cyclic chemotherapy, 5 with VAD (vincristine, adriamycin, dexamethasone) and 2 with MP (melphalan, prednisone). Five of 8 Non-Hodgkin's lymphoma (NHL) patients were in the chemotherapy period, 2 with CVP (cyclophosphamide, vincristine, prednisone) and 3 with CHOP (cyclophosphamide, adriamycin, vincristine, prednisone). One patient was being followed without chemotherapy after 9 cycles CHOP therapy.

P. carinii oocysts detected by indirect immunofluorescence test (Monofluo Kit *P. carinii* Sanofi Diagnostics Pasteur, France).

P. carinii positive patients were treated with TMP-SMX at a daily dose of 15 mg/kg TMP and 75 mg/kg SMX (maximum daily dose was 640 mg for TMP/3200 mg for SMX) for 21 days.

Logistic Regression analysis was applied in order to detect the risk factors effecting PCP (steroid usage, neutropenia duration, severe or mild neutropenia and disease types). Chi-Square test was used for detecting one by one relations among risk factors and PCP (Patients who received fludarabine therapy were not included into the statistical analysis. Neutropenia was divided into two groups; patients with mild and moderate neutropenia were considered as one group).

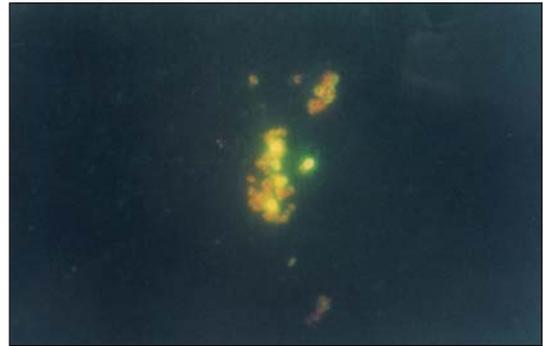


Figure 1. Fluorescent microscopic images of *P. carinii* oocysts (x 200).

Mann-Whitney U test were used for comparing ages.

RESULTS

Thirty-three specimens were evaluated from 31 patients. *P. carinii* oocysts (Figure 1) were detected in 12 (38.7%) patients (3 female, 9 male) with haematological malignancies (Table 2). The median age was 43.5 years (range: 16-68 years) in patients with PCP and 53 years (Range: 16-72 years) in patients without PCP ($p > 0.05$). Seventeen specimens from 16 AL patients were evaluated and *P. carinii* oocysts were detected in 8 (50%) of them. Five of 8 AL (62.5%) patients with PCP were in relapse AL and 3 patients had de novo AL. *P. carinii* oocysts were also detected in three patients with MM (42.8%) and 1 pati-

Table 2. The distribution of *P. carinii* in haematological malignancies

	PCP (+) (%)	PCP (-) (%)	Total
De novo AL	3 (37.5)	5 (62.5)	8
Relapsed AL	5 (62.5)	3 (37.5)	8
MM	3 (42.9)	4 (57.1)	7
NHL	1 (12.5)	7 (87.5)	8
Corticosteroid usage	4 (33.3)	8 (66.7)	12
HD ARA-C	5 (62.5)	3 (37.5)	8
Severe neutropenia	6 (46.2)	7 (53.8)	13
Mild-moderate neutropenia	4 (44.4)	5 (55.6)	9
Prolonged neutropenia	4 (57.1)	3 (42.9)	7

AL: Acute leukemia, NHL: Non-Hodgkin's lymphoma, MM: Multiple myeloma, HD-ARA-C: High dose cytosine arabinoside.

ent with NHL (12.5%). Four patients with PCP were receiving intermittent corticosteroid therapy, 4 patients had got HD ARA-C therapy. The latter 4 patients had relapsed AL also. Ten patients with PCP had neutropenia (6 severe), 4 patients had severe and prolonged neutropenia. The distribution of *P. carinii* positivity according to disease and the other variabilities were given in Table 2.

Positive results were obtained mostly from bronchial lavage fluid (43%), followed by pleural fluid and sputum (33% and 31%) respectively.

Statistically significant relation was not found between the PCP positivity and potential risk including steroid usage, neutropenia duration, severe or mild neutropenia and disease types in univariate analysis and logistic regression analysis ($p > 0.05$).

Six patients with PCP did not respond to therapy and died (50%), 4 of them were relapsed AL.

DISCUSSION

Patients with haematological malignancies especially Hodgkin's and non-Hodgkin lymphoma and acute leukemia are mostly sensitive to PCP^[5]. PCP is not an infrequent cause of death in these patients either. Defense against *P. carinii* is maintained primarily by cellular immunity but neutrophil count and function are also important. It was also shown that lymphopenia has been a risk factor for *P. carinii* infection and the rate of PCP is directly related with CD4+ cell counts^[6,7]. Hence, T cell depressed patients or patients with T cell malignancies are the most sensitive patient groups^[8,9]. Similarly corticosteroids and the drugs which induce T cell depletion such as cyclosporine-A and fludarabine increase the incidence of PCP^[10-13]. Humoral immunity appears to have a limited role in host defense against PC, but recent experimental evidence shows that B cells and antibodies may also contribute to host defense against PC^[4,14].

It was previously shown that the detection of *P. carinii* in the sputum may not always be able and negative results do not exclude PCP^[4]. If bronchoalveolar lavage fluid could be obtained from all of the patients in our study, the rate of positivity should be increased. One of our AL case's bronchial lavage fluid revealed positive *P. carinii* while his sputum was negative.

In the present study, *P. carinii* oocytes were detected in 8 (50%) AL patients. The symptoms of disease in most of our acute leukemia patients arised after the chemotherapy and when the patients were in leukopenia. Neutropenia was not statistically a risk factor according to our study. Although not significant, patients with HD ARA-C therapy and prolonged neutropenia had higher rates of PCP. These patients were also in profound lymphopenia at the time of neutropenia (not documented). Relapsed AL patients are probably more sensitive to PC than the other patients and death occurred mostly in this group. Severe neutropenia may increase the PC rate in these patients and probably, impairment of cellular immunity due to previous chemotherapies (induction and consolidation with high dose ARA-C) may have an additive effect on neutropenia, hence, increase rates of PC infection.

The rate of PCP in NHL patients (12.5%) were lower than AL and MM patients in present study and our PCP rates in NHL patients were not consisted with previous studies which showed lower rates in AL and higher in NHL^[15]. The difference may be due to the low number of NHL patients, patients with relapsed AL, the diversity of obtained specimens and the technic that was used in this study.

According to our study multiple myeloma patients were also sensitive to PCP (42.8%). All of the MM patients were in the chemotherapy period and they had mild to moderate neutropenia. We could not find the documented PCP rates in symptomatic MM patients except case reports^[16,17].

According to our study, the drugs like corticosteroids and ARA-C did not increase the incidence of PCP significantly in patients with haematologic malignancies. We couldn't find previously documented data about ARA-C administration and its effects on PCP rates. Although it was not significant the incidence of PCP was found to be higher in patients who treated with HD ARA-C (62.5%) in this study. Profound myelosuppression with severe neutropenia and lymphopenia probably the cause of higher rates. Corticosteroid administration has been a risk factor but, in present study the rates of PCP were lower in patients receiving corticosteroids. Probably the intermittent administration of corticosteroids may have the preventing effect on these patients.

As a result, PCP is not infrequent in acute leukemia and multiple myeloma patients with respiratory symptoms. We can suggest that chemoprophylaxis may be considered for patients with relapsed acute leukemia who had treated with especially HD ARA-C therapy when they were in prolonged neutropenia. Further prospective studies with large patients groups will be required to confirm our findings.

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