The Ulster Medical Journal, Volume 67, No. 2, pp. 104-109, November 1998.

A cluster of suspected pneumocystis carinii pneumonia following intensive chemotherapy in a Belfast haematology unit

Y L Ong, F G C Jones

Accepted 25 June 1998

SUMMARY

Five cases of pneumocystis carinii pneumonia were diagnosed in adult patients following intensive chemotherapy in the Royal Group of Hospitals haematology unit, Belfast, within a space of six months. The common features and the risk factors contributing to the increased susceptibility of these patients are discussed, as are the likely mechanisms of transmission of infection.

INTRODUCTION

Pneumocystis carinii pneumonia (PCP) is a potentially life-threatening opportunistic infection. It was first recognised in Europe as a distinct clinical entity in children immune-suppressed by malnourishment during the Second World War. There was renewed interest in pneumocystis in the early 1980s when it became recognised as the AIDS defining pulmonary infection. Pneumocystis is a unicellular organism discovered by Chagas in 1909. It was subsequently shown to be a fungus as a result of RNA sequencing.[1] There are recent reports of increasing incidence of this infection following organ transplantation due to high-dose immuno-suppressive agents.

We report a cluster of five suspected cases of pneumocystis carinii pneumonia in the regional haematology unit, Royal Group of Hospitals, Belfast, between August 1995 and February 1996. Case records for these patients were retrieved and studied in detail. Clinical course, treatment and survival outcome were followed up. We also review the literature on this subject and compare it with our own experience.

Patient 1 (index case)

A 28-year-old male with acute monocytic leukaemia presented with lethargy and bone pain. He achieved complete remission following the first course of chemotherapy MAE 3+10+5 (Mitozantrone 12 mg/m^2 daily i.v. on days 1, 3 and 5; cytarabine 100 mg/m^2 12 hourly i.v. on days 1-10 inclusive, and etoposide 100 mg/m^2 daily i.v. on days 1-5 inclusive). He experienced severe nausea during chemotherapy unrelieved by ondansetron, domperidone, cyclizine or metoclopramide. Dexamethasone 4 mg 8-hourly was subsequently used with good effect.

Dexamethasone was also used prophylactically with his second course MAE 3+8+5. He subsequently developed febrile neutropenia. Central and peripheral blood cultures were taken prior to commencing teicoplanin, ciprofloxacin and netilmicin. He was allergic to penicillin. Fluconazole 200 mg i.v. daily was added two days later when his pyrexia failed to settle. Coliform bacilli were isolated from blood culture. Sensitivity testing confirmed that he was receiving the right antibacterial therapy.

However, two weeks later, he remained pyrexic despite bone marrow recovery as indicated by the rise in his leukocyte count. This was followed by a rapid clinical deterioration. He developed a non productive cough, experienced shortness of breath

Department of Haematology, Royal Group of Hospitals NHS Trust, Belfast, Northern Ireland.

Y L Ong, MB, BCh, MRCP, Specialist Registrar, Haematology.

F G C Jones, MB, BCh, FRCP, FRCPath, Consultant Haematologist.

Correspondence to: Dr Jones.

at rest and had difficulty in drawing a deep breath. He was cyanosed, tachypnoeic with sinus tachycardia 120 bpm. Chest expansion and air entry were restricted bilaterally. There were fine crepitations in the midzones and bases. Chest radiograph revealed bilateral interstitial hazy shadowing consistent with PCP, compared to a normal chest radiograph four days earlier. Arterial blood gas analysis was contraindicated by the thrombocytopenia. Broncho-alveolar lavage was discussed but deemed inexpedient as the bronchoscopy unit was located in the Belfast City Hospital and a transfer journey by an ambulance would be required. He was hypoxic and dependent on high-flow oxygen. Decision was made to start empirical treatment without delay. Intravenous co-trimoxazole (trimethoprim-sulfamethoxazole) at 1.92 gram q.d.s. and dexamethasone 10 mg daily was started immediately. The use of high-flow oxygen, saline nebuliser and chest physiotherapy failed to induce any sputum for examination. Within 48 hours, there was significant clinical improvement, accompanied by resolution on the chest radiograph. Two days later he was well enough to be discharged on high dose oral co- trimoxazole.

He continued on co-trimoxazole at the prophylactic dose of 480 mg b.d. thrice weekly with no recurrence of PCP at 14 months. Unfortunately, he succumbed to the acute leukaemia 15 months following diagnosis.

Patient 2

A 26-year-old male with acute lymphoblastic leukaemia developed an acute respiratory illness after two months of intensive multidrug cytotoxic regime containing high dose prednisolone (UKALL 12 MRC protocol). Initially, he was pyrexic without respiratory symptoms. Intravenous antibacterial treatment with benzyl penicillin, netilmicin and ciprofloxacin was commenced following blood cultures. When pyrexia failed to settle after 48 hours, he was switched to second line ceftazidime and amikacin. Intravenous fluconazole was subsequently added. However, he soon developed dry cough and shortness of breath. He was cyanosed with bronchial breathing in the right lung, (PO_2 31 mmHg, PCO_2 35 mmHg). Chest radiograph showed diffuse bilateral patchy shadowing suggestive of PCP. He responded to high dose co-trimoxazole and adjuvant corticosteroid within 48 hours. He was doing well at 37 months follow-up.

Patient 3

A 29 year old male with acute lymphoblastic leukaemia developed dry cough, dyspnoea and recurrent pyrexia eight months into chemotherapy as per the UKALL 12 protocol. Chest radiograph revealed perihilar shadowing suggestive of PCP. High dose co-trimoxazole and adjuvant steroid resulted in rapid resolution of symptoms. An allogeneic bone marrow transplantation was performed. The patient was well at 42 months follow-up.

Patient 4

A 38-year-old male with chronic psychosis presented with a large cervical mass shown to be high-grade non-Hodgkins lymphoma. After five courses of 'CHOP' chemotherapy (cyclophosphamide 750 mg/m^2, doxorubicin 50 mg/m^2, vincristine 1.4 mg/m^2 and prednisolone 40 mg/m^2), he became unwell, with pyrexia and cough productive of green sputum. He smoked heavily and refused food, resulting in significant weight loss. His lactate dehydrogenase level (LDH) which had become normal following cytotoxic chemotherapy became raised once again, raising suspicion of a lymphoma recurrence. Chest radiograph was normal. CT scan which was carried out to reassess his lymphoma surprisingly revealed several areas of bilateral ground-glass opacity suggestive of PCP. High dose co-trimoxazole was instituted immediately. His pyrexia settled.

Patient 5

A 36-year-old male with multiple myeloma was treated with four courses of chemotherapy (vincristine, adriamycin and dexamethasone) followed by allogeneic bone marrow transplantation. Methotrexate, cyclosporin and prednisolone were used to prevent graft versus host disease. He received cytomegalovirus specific intravenous immunoglobulin and prophylactic co-trimoxazole. He experienced occasional nausea and vomiting after transplantation but tried his best to comply with his medication.

Ten weeks later he became unwell, with shortness of breath on exertion, pyrexia and cough productive of purulent sputum. On examination he had sinus tachycardia and basal crepitations at both lung bases. Chest radiograph showed bilateral chronic inflammatory changes. Computed tomography revealed peripheral ill-

TABLE I

Lactate dehydrogenase level at different clinical stages illustrating a transient elevation during infection with PCP

LDH level u/l	*At presentation*	*Post-chemotherapy*	*During PCP*	*Post-high dose Co-trimoxazole*
Patient 1 (AML)	2023	250	704	312
Patient 2 (ALL)	1939	758	1601	477
Patient 3 (ALL)	1749	378	1296	502
Patient 4 (NHL)	2702	684	1143	415
Patient 5 (MM)		989	1161	963

(LDH normal range in our laboratory 360-720 u/l)

TABLE II

Haematological parameters at diagnosis of PCP showing recovery of neutrophil count but persistent lymphopenia following myelosuppressive chemotherapy

	Total leucocyte 10^3/ul	*Neutrophil 10^3/ul*	*Lymphocyte 10^3/ul*	*Monocyte 10^3/ul*	*Eosinophil 10^3/ul*
Patient 1 (AML)	4.9	3.38	0.59	0.69	0
Patient 2 (ALL)	2.7	2.51	0.11	0.03	0.05
Patient 3 (ALL)	12.7	9.9	1.65	0.76	0.38
Patient 4 (NHL)	5.7	4.1	0.86	0.63	0.06
Patient 5 (MM)	3.1	2.79	0.09	0.16	0.03

Normal range (10^3/ul): Total leucocyte 4-11; Neutrophil 1.7-6.1; Lymphocyte 1-3.2; Monocyte 0.2-0.6; Eosinophil 0.03-0.46

defined opacities and interstitial changes in the peribronchial region and mid zones. Penicillin resistant *streptococcus pneumoniae* was isolated from blood culture. It was sensitive to cefotaxime and he was treated accordingly. Liposomal amphotericin was added later when his pyrexia failed to settle. Fluorescent antibody testing of the sputum for PC was positive. He was commenced on high-dose co-trimoxazole with dose modification for impaired renal function. He made a good recovery and remained well at 38-months follow-up.

The common features of the above patients are summarised below:

1. All had intensive chemotherapy which had been started at least 6 weeks before developing PCP.
2. All had been on a corticosteroid.
3. All showed a transient elevation in lactate dehydrogenase level (LDH) during pneumocystis infection without evidence of underlying disease recurrence (Table I).

4. All failed to respond to initial broad spectrum anti-bacterial and anti-fungal agents but improved after high dose co-trimoxazole and adjuvant corticosteroid.
5. A recovering leukocyte count after cytotoxic treatment did not curtail the respiratory illness.
6. All had been in the same four-bedded male bay or in the cubicles opposite, which were managed by the same nursing team (the nursing responsibility in the ward is divided into team A and team B). Patients 1, 4 and 5 were hospitalised at around the same time and developed PCP within a space of 2 months. Patients 2 and 3 started induction chemotherapy in the same month. They subsequently developed PCP one month apart. All cases occurred within a 6-month period. All patients had spent many months in and out of haematology ward receiving treatment as dictated by current cytotoxic protocol. In the case of patient 4 with lymphoma, his chronic psychosis and social circumstances necessitated in-patient supervision of treatment, which otherwise would have been administered as an outpatient.

DISCUSSION

The data on the incidence of PCP in haemato-oncology patients is quite scanty. A report in 1995 followed up 214 adult patients with acute lymphoblastic leukaemia (ALL). 5% were diagnosed with PCP at some point during the two years of treatment.[2] Another group of investigators from Helsinki looked for PCP in 29 new adult ALL and 44 acute myeloid leukaemia (AML) from July 1990 to December 1993. PCP prophylaxis was not included in the therapeutic protocol. 24% ALL and none with AML developed PCP.[3] This incidence is similar to childhood ALL in which 21% developed PCP prior to co-trimoxazole prophylaxis.[4]

All patients reported above had been started on intensive cytotoxic regime and corticosteroid at least 6 weeks prior to the onset of their respiratory illness. To the best of our knowledge, PCP has never been reported in untreated patients with leukaemia or lymphoma. This suggests the patients' susceptibility to PCP is more closely related to the type and the intensity of treatment than to their haematological malignancy. Over the years, little has changed in the treatment of non-Hodgkin's lymphoma. CHOP type regime remains the cornerstone, which is less intensive and the duration of leucopenia is short compared to the treatment protocols for acute lymphoid and myeloid leukaemias. However, patient 4 with non-Hodgkin's lymphoma illustrates that malnutrition and heavy smoking may be adding to his susceptibility to pneumocystis infection. He suffers from chronic schizophrenia and his behavioural problems had contributed to his eating disorder and subsequent weight loss.

The chest radiograph in PCP maybe normal and hence unhelpful in the early stages. It typically shows bilateral perihilar interstitial infiltrates, progressing to diffuse confluent alveolar shadowing as patients deteriorate clinically. Our experience with patients 4 and 5 above indicates that CT scanning may be more sensitive than plain x-ray in revealing the interstitial changes in early or subacute PCP.

Serum LDH level is a non specific test useful for monitoring the cell turnover rate and the disease activity in malignant haematological disorders. It has also been noted to be raised in HIV positive patients who develop pneumocystosis. Hence an increase in the LDH level in patients whose underlying disease has attained complete remission should alert the clinician to the possibility of pneumocystis infection.

In general, most patients with bacterial and fungal infections associated with cytotoxic therapy show clinical improvement coinciding with a rise in their leukocyte counts from their lowest level. From our experience, the recovery of haemato-logical parameters, notably the neutrophil count (Table II) following chemotherapy, did not prevent or curtail PCP as would be expected in bacterial infections. Absolute lymphopenia was found in 4 out of the 5 patients at diagnosis of PCP. This supports the view that cell-mediated immunity is most important for protection from PC. Although the lymphocyte subsets were not measured in our patients, solid data from HIV patients had shown that the risk of PCP correlates with CD4 T lymphocyte count of <200/ul (multicentre AIDS Cohort Study). Limited reports in cancer patients suggest a similar relationship.[5,6] However, the predictive value of CD4 count has not been evaluated in non-HIV patients.

Most of the experience in managing PCP also came from HIV patients. Some clinicians strongly advocate that all who present with symptoms and chest x-ray or arterial blood gas findings

suspicious of PCP should have a bronchoscopy to demonstrate the presence of PC in bronchial secretions or tissue. Others have suggested that such patients may be treated empirically, reserving bronchoscopy for those with atypical presentations and those who do not respond or deteriorate on specific therapy.[7] In clinical practice both strategies seem equally effective.[8] Many centres in UK and USA treat PCP empirically.[9]

Exercise-induced arterial desaturation detected by oximetry in patients with normal resting PaO_2 may help to detect PCP. In the lung function tests, the carbon monoxide transfer factor (TLCO), total lung capacity and forced vital capacity may be reduced, whereas peak expiratory flow and forced expiratory volume in 1 second are frequently normal. A reduction in the TLCO is the most sensitive marker of PCP but this lacks specificity as it is also decreased in bacterial infections. We need a sensitive, reliable and non-invasive tool for early diagnosis of PCP, as patients with malignant haematological conditions immune-compromised by intensive chemotherapy can deteriorate very rapidly. Sputum induction is uncomfortable and the yield is poor. Bronchoalveolar lavage is not always possible as these patients may be too tachypnoeic and hypoxic. Transbronchial biopsy may be contraindicated by thrombocytopenia or coagulopathy. Open lung biopsy, though the most sensitive and specific, is also the most hazardous. Many clinicians believe that transbronchial and open lung biopsies have little to add to bronchoscopy and bronchoalveolar lavage. In practice, empirical treatment must be started without delay. Recent studies showed that it is possible to amplify pneumocystis carinii DNA by PCR directly from blood and nasopharyngeal aspirates of PCP patients. [10,11] However, cost and availability are limiting factors. There is no established culture system for pneumocystis carinii that would allow traditional antimicrobial sensitivity testing. This and a serologic test that will distinguish recent from past infections are needed.

PCP is fatal in almost all cases if left untreated. Adjuvant use of steroid has contributed to decreased mortality rate and has reduced the need for assisted ventilation in the most severe cases. The mechanisms for this paradoxical response may be attributed to a reduction in the cellular infiltrates within alveolar spaces, allowing better gas exchange and improving chest expansion.

Patient 5 illustrates a well-recognised complication following bone marrow transplantation, that of functional hyposplenism related to total body irradiation. This predisposed the individual to infection by capsulated bacteria, especially pneumococci. The superinfection with pneumococci had enabled production of sufficient amount of sputum to allow confirmation of PCP by fluorescent antibody testing. Although he had been on prophylactic co-trimoxazole since his bone marrow transplant, his susceptibility to PCP was probably increased as a result of hyposplenism.

It is possible that PCP in immune-compromised patients arises by reactivation of a latent asymptomatic infection acquired in childhood. This hypothesis is supported by the finding of antibodies to PC in most healthy children and adults.[12] Immunosuppression in later life may lead to clinical manifestations. However, over the years a steady flow of reports has described clusters of PCP cases not readily explained by reactivation of latent infections. Recent studies have suggested that the duration of latency is very limited, usually less than one year.[13,14] There may be an alternative explanation.

Although person-to-person transmission of PC is yet to be proven in human, we are concerned about the clustering of cases in the ward within a space of 6 months. PC DNA has been identified from ambient air sampled from rural Oxfordshire in the UK,[15] and from rooms of animals and patients with PCP in United States.[16] Recent studies have demonstrated genetic variation in PCR – amplified pneumocystis carinii DNA from the lungs of patients during recurrent PCP episodes.[17] All these data indicate that PC is caused by airborne organisms and that person-to-person transmission of pneumocystis carinii is possible. At least some cases of PCP are due to acquisition of new infection from an exogenous source rather than relapse of an existing infection. This has significant implications on the management of immune-compromised patients in the haematology ward. Studies are needed to decide whether case to case transmission contributes to infection significantly more than airborne sources in the environment. Consequently, preventative measures and decontamination procedures might be drawn up

to protect patients. Until the epidemiologic features and mode of acquisition of PC are better understood, antimicrobial drugs remain the only available method for PCP prophylaxis. Some haematologists are reluctant to use co-trimoxazole for fear of exacerbating myelosuppression and inducing antimicrobial resistance. Besides, pneumocystis infection in non-HIV haematology patients appears to be sufficiently uncommon to justify prolonged use of co-trimoxazole. We need to define the risk factors in order to target a subgroup of patients for PCP prophylaxis after institution of cytotoxic therapy.

The risk factors we have identified are:

1. Lymphoproliferative malignancies after intensive chemotherapy.
2. Corticosteroid therapy.
3. Bone marrow transplantation.
4. Lymphopenia.
5. Poor nutrition and possibly smoking.

In conclusion, PCP is a preventable complication in patients treated with cytotoxic chemotherapy and corticosteroid. It should be considered in the differential diagnosis of pneumonia. A rise in LDH level in patients who have attained remission from their haematological malignancy should prompt a search for PC, as rapid deterioration may ensue if treatment is delayed. Prophylaxis for PCP is now routinely started in our unit in selected high-risk patients approximately one month following institution of intensive chemotherapy.

REFERENCES

1. Stringer J R. The identity of Pneumocystis carinii: not a single protozoan, but a diverse group of exotic fungi. *Infect Agents Dis* 1993; **2**: 109-17.
2. Larson R A, Dodge R K, Burns C P, et al. A five-drug remission induction regimen with intensive consolidation for adults with Acute Lymphoblastic Leukaemia: cancer and leukaemia group B study 8811. *Blood* 1995; **85**: 2025-37.
3. Lyytikainen O, Elonen E, Lautenschlager I, et al. Pneumocystis carinii pneumonia in adults with acute leukemia: is there a need for primary prophylaxis? *Eur J Haematol* 1996; **56**: 188-9.
4. Hughes W T, Kuhn S, Chaudhary S, et al. Successful chemoprophylaxis for Pneumocystis carinii pneumonites. *N Engl J Med* 1977; **297**: 1419-26.
5. Siminski J, Kidd P, Phillips G D, et al: Reversed helper/suppresser T-lymphocyte ratio in bronchoalveolar lavage fluid from patients with breast cancer and Pneumocystis carinii pneumonia. *Am Rev Respir Dis* 1991; **143**: 437-40.
6. Castagnola E, Dini G, Lanino E, et al. Low CD4 lymphocyte count in a patient with Pneumocystis carinii pneumonia after autologous bone marrow transplantation. *Bone Marrow Transplant* 1995; **15**: 977-8.
7. Miller R F, Millar A B, Weller I V D, Semple S J G. Empirical treatment without bronchoscopy for Pneumocystis carinii pneumonia in the acquired immunedeficiency syndrome. Thorax 1989; 44: 559-64.
8. Tu J V, Biem H J, Detsky A S. Bronchoscopy versus empirical therapy in HIV-infected patients with presumptive Pneumocystis carinii pneumonia: a decision analysis. *Am Rev Respir Dis* 1993; **148**: 370-7.
9. Bennett C L, Horner R D, Weinstein R A, et al. Empirically treated Pneumocystis carinii pneumonia in Los Angeles, Chicago and Miami: 1987-90. *J Infect Dis* 1995; **172**: 312-15.
10. Atzori C, Lu J-J, Jiang B, et al. Diagnosis of Pneumocystis carinii pneumonia in AIDS patients by using polymerase chain reactions on serum specimens. *J Infect Dis* 1995; **172**: 1623-6.
11. Richards C G M, Wakefield A E, Mitchell C D. Detection of pneumocystis DNA in nasopharyngeal aspirates of leukaemic infants with pneumonia. Arch Dis Child 1994; 71: 254-5.
12. Peglow S L, Smulian A G, Linke M J, et al. Serologic responses to *Pneumocystis carinii* antigens in health and disease. *J Infect Dis* 1990; **161**: 296-306.
13. Chen W, Gigliotti F, Harmsen A G. Latency is not an inevitable outcome of infection with Pneumocystis carinii. *Infect Immun* 1993; **61**: 5406-9.
14. Vargas S L, Hughes W T, Wakefield A E, Oz H S. Limited persistence in and subsequent elimination of Pneumocystis carinii from the lungs after Pneumocystis carinii pneumonia. *J Infect Dis* 1995; **172**: 506-10.
15. Wakefield A E. Detection of DNA sequences identical to Pneumocystis carinii in samples of ambient air. *J Eukaryst Microbiol* 1994; **41**: 116S.
16. Bartlett M S, Lee C H, Lu J-J, et al. Pneumocystis carinii detected in air. *J Eukaryst Microbiol* 1994; **41**: 75S.
17. Keely S P, Stringer J R, Baughman R P, Linke M J, Walzer P D, Smulian A G. Genetic variation among *Pneumocystis carinii hominis* isolates in recurrent pneumocystosis. *J Infect Dis* 1995; **172**: 595-8.