Pneumocystis carinii pneumonia in Hong Kong: a 10 year retrospective study

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A retrospective review was performed of patients diagnosed with *Pneumocystis carinii* pneumonia (PCP) from 1994 to 2003 at the Prince of Wales Hospital in Hong Kong. Eighteen patients were identified. Six (33·3 %) were co-infected with human immunodeficiency virus (HIV). The remaining 12 non-HIV-infected patients had underlying diseases: three post-renal transplant recipients, three with haematological malignancies, two with auto-immune diseases, two with renal diseases, one with hepatocellular carcinoma and one with congenital cytomegalovirus disease. Cytomegalovirus co-infection was observed in four patients. All patients received cotrimoxazole therapy, with intolerance observed in four of them, including one with glucose-6-phosphate dehydrogenase deficiency, two with repeated vomiting and one with renal impairment. Overall crude mortality was 33·3 %. The results suggested that, apart from being a common infection for patients with HIV infection, PCP can occur during the course of many immunosuppressive diseases and therapies. The mortality of PCP was high despite appropriate treatment. Chemoprophylaxis should be considered in populations at risk.

INTRODUCTION

Pneumocystis carinii is an opportunistic fungus capable of causing life-threatening pneumonia in patients with impaired cellular immunity (Cailliez *et al.*, 1996; Cunha, 2001). It is one of the commonly encountered opportunistic infections in human immunodeficiency virus (HIV)-infected patients. Primary and secondary prophylaxis have been advocated to prevent the infection in AIDS patients (Barry & Johnson, 2001; Phair *et al.*, 1990; Schliep & Yarrish, 1999). In contrast, much less is known about *Pneumocystis carinii* pneumonia (PCP) in non-HIV-infected patients. Hong Kong has a very low prevalence of HIV infection, with an estimated prevalence of less than 0·1 % (WHO, 1999). Therefore, the spectrum of PCP infection may be different from populations where the HIV infection rate is higher. The aim of this study was to analyse the characteristics of patients suffering from PCP in Hong Kong through a retrospective 10-year case review.

METHODS

A retrospective case review was conducted of patients suffering from PCP at the Prince of Wales Hospital in Hong Kong from 1994 to 2003. Cases of PCP were identified from the laboratory log from the Microbiology Department. The laboratory utilized a toluidine blue O staining method to identify the fungus from bronchoalveolar

lavage specimens. Only cases with detection of *Pneumocystis carinii* by this method were included. We focused on the epidemiology, underlying diseases, treatment and mortality of these PCP patients. Results were entered into a standard log and then analysed.

RESULTS AND DISCUSSION

Eighteen patients with PCP were identified over the 10 year period, of whom 14 were males (male/female 3·5:1). The mean age of the patients was 42·5 years (range 4 months to 67 years); the mean age of the female patients was 49·5 years and that of the male patients was 40·6 years.

Six (33·3 %) patients were HIV positive; all of them were males. Only two of them were aware of their HIV-seropositive status prior to their admission with PCP. One had a CD4 count less than 100 cells μl^{-1} . The remaining four patients were diagnosed to have HIV infection during admission with PCP.

All HIV-seronegative patients ($n=12$) had underlying diseases. Three were renal-transplant recipients, three had haematological malignancies (two non-Hodgkin's lymphoma, one T-cell lymphoma), two with autoimmune diseases (one systemic lupus erythematosus, one dermatomyositis), two with renal diseases (one nephrotic syndrome, one glomerulonephritis), one with advanced hepatocellular carcinoma and one was an infant with congenital cytomegalovirus (CMV) disease, together with necrotizing enterocolitis.

All HIV-seronegative patients with PCP (except the infant) were given immunosuppressive therapies at the time of

Abbreviations: CMV, cytomegalovirus; G6PD, glucose-6-phosphate dehydrogenase; HIV, human immunodeficiency virus; PCP, *Pneumocystis carinii* pneumonia.

diagnosis of PCP, including prednisolone (daily dose range 15–100 mg), cyclophosphamide, cyclosporine A, azathioprine, doxorubicin, vincristine, chlorambucil, cytarabine, mercaptopurine and methotrexate (Table 1).

Ten of the 12 HIV-seronegative patients acquired PCP within 7 months of the diagnosis of the underlying disease. In particular, all three renal-transplant recipients had commenced immunosuppressive therapy less than 6 months before the diagnosis of PCP.

All PCP patients were started with cotrimoxazole. The commonest dose used was 3840 mg per day ($n=6$) in divided dose. For adult patients, the highest daily dose of cotrimoxazole used was 9600 mg, while the lowest dose was 960 mg. The only infant was given 360 mg. Of the adult patients, seven were given steroid adjuvant therapy, including prednisolone in five patients and hydrocortisone in two patients. One patient was switched to pentamidine after 4 days of cotrimoxazole (3840 mg per day) treatment due to slow clinical improvement. One patient was tested to have glucose-6-phosphate dehydrogenase (G6PD) deficiency. He was initially treated with cotrimoxazole, but subsequently changed to trimethoprim after just one dose of cotrimoxazole was given. No drug-induced haemolysis was detected in this patient. Two patients suffered from repeated vomiting while on treatment (one on cotrimoxazole, one on trimethoprim), but managed to continue with their therapy. Another patient initially treated with cotrimoxazole had to decrease the dosage from 3600 mg per day to 2400 mg per day due to renal impairment. Severe side effects such as Steven Johnson syndrome were not observed in any of the patients.

Table 1. Underlying diseases and immunosuppressive agents used in HIV-seronegative PCP patients

Abbreviations: Ara-C, cytarabine; AZA, azathioprine; CLB, chlorambucil; CTX, cyclophosphamide; CyA, cyclosporine A; DOX, doxorubicin; 6-MP, mercaptopurine; MTX, methotrexate; Pred, prednisolone; VCR, vincristine.

Case	Underlying disease	Immunosuppressive agents used
1, 2	Non-Hodgkin's lymphoma	Pred, CTX, DOX, VCR
3, 4, 5	Renal-transplant recipient	Pred, CyA, AZA
6	T-cell lymphoma	Pred, CTX, Ara-C, 6-MP, MTX
7	Dermatomyositis	Pred
8	Systemic lupus erythematosus	Pred, CTX
9	Hepatocellular carcinoma	Pred, DOX
10	Glomerulonephritis	Pred, CTX
11	Nephrotic syndrome	Pred, CLB
12	Congenital CMV infection	None

None of the 18 patients was given primary prophylaxis. Only one patient was given secondary prophylaxis, with pentamidine inhalation.

Two patients were observed to have concomitant bacterial pneumonia (one with *Pseudomonas aeruginosa* and the other with *Streptococcus pneumoniae*). Three patients had concomitant CMV pneumonitis. Five patients required admission to the intensive care unit and four of them required ventilation care. Six patients died, and all were HIV seronegative. Overall crude mortality was 33.3 %. Patients with concomitant bacterial or viral pneumonia had a mortality of 40 %. Of those requiring intensive care, the mortality was 80 %. For the group of patients treated with steroid adjuvant therapy, the mortality was 43 %. The mean age of the patients who died was 51.7 years and that of the survivor group was 37.9 years.

After recovery from PCP, all HIV-seronegative patients ($n=12$) were followed up in the Prince of Wales Hospital. No recurrence of PCP was observed during the follow-up period (mean duration 3.5 years; range 4 months to 8 years). The six HIV-infected patients were referred to the AIDS Unit of the Department of Health of Hong Kong; hence, no information on recurrence rate is available for this group.

In our study, of the 18 PCP patients identified, six were HIV co-infected. This figure was much lower than those reported by other studies. One 10 year case-review study done in Sydney found that 69.6 % of PCP patients had HIV co-infection (Gerrard, 1995). This difference was probably due to the fact that the prevalence of HIV infection in Hong Kong was very low.

The age distribution of the patients follows a normal distribution curve, with a peak at the age range of 40–49 years. This probably reflected the general epidemiology of the underlying diseases in our patients; for example, chronic renal failure patients that required renal transplantation and systemic lupus erythematosus. However, the number of patients is too small to draw a definitive statistical conclusion. One of the cases was an infant with congenital CMV infection. This infant was regarded as otherwise immunocompetent and had been reported by Leung *et al.* (2000). They proposed that the co-infection of CMV and trace element (zinc) deficiency may have compromised the infant's immune defence.

The underlying risk factors of PCP found in our study were similar to those reported in other studies (Arend *et al.*, 1995; Sepkowitz, 2002; Roblot *et al.*, 2002; Saksasithon *et al.*, 2003). All HIV-seronegative adult patients had chronic underlying diseases that required various immunosuppressive therapies. Studies have proven that chronic steroid use predisposes patients to a variety of infections by impairing their host defence mechanisms. A controlled trial showed that, with systemic steroid use, the risk of infection increases with the dose and duration of therapy. The relative risk of

infection was 1.6 times higher in steroid-treated patients. The rate of infection was not increased in patients receiving prednisolone at less than 10 mg day⁻¹ (Stuck *et al.*, 1989; Klein *et al.*, 2001). Although steroids can be used in the treatment of a wide spectrum of diseases, including organ rejection therapy and autoimmune diseases, one should be aware of the increased risk of infection when larger doses are being used.

Despite all of the underlying risk factors, none of the patients was receiving primary prophylaxis. This is particularly worrying as two of the patients were known to be HIV seropositive prior to the presentation of PCP, and one of them had a CD4 count of less than 100 cells µl⁻¹. In this era of highly active antiretroviral therapy (HAART) and effective chemoprophylaxis, PCP could probably have been prevented in these patients with appropriate prophylaxis and treatment (Klein *et al.*, 1992; Vilar *et al.*, 1999; Palella *et al.*, 1998). As four other HIV-infected patients were only diagnosed together with the presentation of PCP, this reflects another worrying aspect of a locality with generally low prevalence of HIV infection, in which the population at high risk of HIV infection are relatively unaware of the risk, resulting in late presentation with the infection (Wong *et al.*, 2003). Chemoprophylaxis has also been shown to be effective in patients with other risk factors, such as cardiac and renal transplant recipients (Higgins *et al.*, 1989; Gordon *et al.*, 1999; Olsen *et al.*, 1993). Since the mortality of PCP remains high even with appropriate treatment, prevention may be the best way to reduce the number of deaths due to this disease.

There were no severe side effects associated with the use of cotrimoxazole observed in our group of patients. Only two of 18 patients failed to continue initial therapy with cotrimoxazole due to intolerance. G6PD deficiency is a relatively common condition in Hong Kong, with an incidence of 4.5 % in males and 0.36 % in females (Li *et al.*, 1999). Only one patient was found to have G6PD deficiency in our studied group. This suggested that cotrimoxazole was a generally well-tolerated medication in our population.

Overall crude mortality in our study was similar to other studies (32–38 %; Gerrard, 1995; Arend *et al.*, 1995; Roblot *et al.*, 2002; Saksasithon *et al.*, 2003). In our series, the mortality was higher in patients with concomitant viral pneumonitis or bacterial pneumonia. This result suggests that respiratory secretions and other appropriate specimens should be sent for the detection of other bacterial or viral pathogens, such as CMV and *Pseudomonas aeruginosa*. This will allow early institution of antibiotic or antiviral treatment to treat concomitant infection, which can further complicate the clinical course or even cause respiratory failure in these patients.

A previous study suggested that corticosteroids should be used for moderate to severe PCP as adjuvant therapy because they could increase survival and prevent the development of acute respiratory failure (Montaner *et al.*,

1990). However, in our study, mortality among patients with steroid adjuvant therapy was slightly higher (43 %) than the overall mortality (33.3 %). This may be due to the small sample size of our study group and therefore a failure to demonstrate a beneficial effect of adjuvant steroids, or it may reflect the increased level of severity of the underlying disease and PCP infection. A larger sample would help to delineate better the nature of the differences in mortality. Likewise, the mean age of patients that died was higher than that of the survivor group. A larger sample with sufficient power may be able to demonstrate whether greater age was a genuine poor prognostic factor of PCP.

All patients who died in this study were not HIV infected. The mean age of HIV-seropositive patients was 34 years, while that of HIV-seronegative group was 46.8 years. It is possible that the difference in mortality was due to the younger age of the group of HIV-infected patients, as well as the severe immunosuppressive effect of the other underlying diseases.

These results suggest that, apart from being a common infection for patients with AIDS, PCP can also occur during the course of many immunosuppressive diseases and therapies. The mortality of PCP was high even with appropriate treatment. Chemoprophylaxis should be considered in populations at risk. Even in a locality with low HIV prevalence, improved education to raise the awareness of the population, with earlier detection of HIV infection, could also be beneficial.

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