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MANAGEMENT OF *PNEUMOCYSTIS CARINII* PNEUMONIA IN PATIENTS WITH CONVENTIONALLY CAUSED IMMUNE SUPPRESSION

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Abstract: Ten non-AIDS patients with *Pneumocystis carinii* pneumonia were studied. While the 2 patients with adult T cell leukemia had longer prodromes, the other 8 patients had acute onset. At presentation a chest radiograph revealed an abnormal bilateral diffuse shadow in all cases. In 8 patients, diagnostic material was obtained by transbronchial lung biopsy and/or bronchoalveolar lavage, and in 2 patients at postmortem. At the time of diagnosis the serum lactate dehydrogenase value was much higher than prior to the acute illness, and the $AaDO_2$ gradient was highly increased: These appear to be useful as markers for an initial diagnosis. Other opportunistic organisms were isolated in 5 patients. The concomitant use of pentamidine and cotrimoxazole was relatively well tolerated, but with a high incidence of treatment failure. Corticosteroids appeared to be effective as an adjunctive therapy.

INTRODUCTION

Pneumocystis carinii pneumonia (PCP) is the most common opportunistic infection which occurs and is a significant cause of death among patients with acquired immunodeficiency syndrome (AIDS). In Japan, the prevalence of AIDS is still low, and PCP is an opportunistic infection seen most frequently in association with certain malignancies or immunosuppressive therapy (Macfarlane and Finch, 1985; Engelberg *et al.*, 1984).

Diagnosis of PCP usually requires invasive methods, such as fiber optic bronchoscopy, although various noninvasive tests, such as chest radiographs and gallium scans, have been used to diagnose this infection (Oka *et al.*, 1985; Cordonnier *et al.*, 1984). Recent studies have shown that the serum LDH value and $P(A\text{-}a)O_2$ gradient might be useful as markers for diagnosis and prognosis of PCP in cases with AIDS (Zaman and White, 1988; Garay and Greene, 1989).

Several studies have demonstrated that pentamidine has a greater incidence of significant adverse reactions, and is no more effective in the treatment of PCP, than cotrimoxazole.

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Table 1 Details of patients with pneumocystis pneumonia

Patient	Sex	Age (years)	Underlying disease	Duration of immunosuppressive therapy	Clinical prodrome and duration	
1	M	63	malignant lymphoma	3 months	cough, fever	3 days
2	M	78	malignant lymphoma	2.5 months	cough,	3 days
3	M	69	adult T cell leukemia	1 week	cough, fever, dyspnea	2 weeks
4	M	47	adult T cell leukemia	2 weeks	cough, fever, dyspnea	3 weeks
5	F	73	lung cancer	4 months	dyspnea	2 days
6	M	32	renal transplantation	10 months	cough, dyspnea	3 days
7	F	53	nephrotic syndrome	2 months	asymptomatic	—
8	M	75	sarcoidosis	2 months	asymptomatic	—
9	M	51	dermatomyositis	7 months	dyspnea	2 days
10	F	44	systemic lupus erythematodes	18 months	asymptomatic	—
Average		58.5 ±14.6		4.9 ±5.2 months		6.9 ±7.0 days

Pentamidine has therefore been used in patients with PCP who have failed to respond to cotrimoxazole or who have sustained adverse reactions to this drug combination. PCP cases from conventionally caused immune suppression are reported to be more fulminant, less likely to relapse, with fewer adverse effects and a greater incidence of treatment failure than those from AIDS (Drake *et al.*, 1985; Salamone and Cunha, 1988; Pearson and Hewlett, 1985; Kluge *et al.*, 1978; Kovacs *et al.*, 1984; Sattler *et al.*, 1988). Therefore in the non-AIDS population, the concomitant use of pentamidine and cotrimoxazole has yet to be examined.

We present our experience in fulminant cases of PCP from conventionally caused immunosuppression admitted to Nagasaki University Hospital during the period 1976-1989.

Patients and Methods

The hospital charts of patients with confirmed PCP between 1976 to 1989 were reviewed. Only those patients with microbiologically documented disease were included. The following data was recorded in all cases: age, sex, underlying disease, use of immunosuppressive drugs, nature and duration of the problem leading to diagnosis, arterial blood gas with calculation of the $P(A\text{-}a)O_2$ gradient, lactate dehydrogenase (LDH) value, chest radiograph findings, treatment, and outcome. Diagnostic procedures included fiber optic bronchoscopy with bronchoalveolar lavage (BAL), transbronchial lung biopsy (TBLB), and postmortem examination. Fiber optic bronchoscopy was performed under local anaesthesia with parenteral sedation. The bronchoscope was wedged into the subsegmental bronchus in the main region of radiographic abnormality. Bronchoalveolar lavage was performed using at least two

Table 2 Diagnostic information

Patient	LDH(IU/L)			PaO_2 (torr) at diagnosis	$P(A-a)O_2$ (torr) at diagnosis	Initial chest radiograph	Definitive diagnosis by
	1-2 months prior to diagnosis	At diagnosis	Increase				
1	478	896	418	38.5(RA)	72.0	bilateral reticular	TBLB
2	587	1,132	545	44.5(RA)	63.5	bilateral reticular and infiltrates	BAL
3	472	663	191	58.2 ($O_2$3l/min)	122	bilateral reticular and infiltrates	BAL
4	—	1,170	—	54.4(RA)	57.0	bilateral reticular and infiltrates	BAL TBLB
5	400	734	334	32.6(RA)	75.6	bilateral reticular	BAL TBLB
6	322	790	468	59.7(RA)	49.0	bilateral reticular	BAL
7	346	1,455	1,109	31.9(RA)	70.1	diffuse ground glass	BAL
8	309	1,723	1,414	32.6(RA)	82.5	bilateral reticular	BAL
9	400	1,173	773	40.0(RA)	74.6	bilateral reticular and infiltrates	post mortem
10	353	589	236	115 ($O_2$11/min)	26.3	bilateral reticular	post mortem
Average	407 ±85.1	1,030 ±347	610 ±391		69.3 ±23.4		

*RA: room air

20 m*l* aliquots of sterile normal saline. Transbronchial lung biopsy was performed under the guidance of fluoroscopy. The fluid obtained by lavage was centrifuged at 1,500 rpm for 5 min. The deposit was spread onto several glass microscope slides and stained to reveal *Pneumocystis carinii* cysts using Gomori's methenamine silver stain. All specimens were also stained by Gram's method. Routine aerobic and anaerobic bacterial cultures were performed on all samples, as were cultures for mycobacteria and fungi. All patients, except for one patient diagnosed as PCP at postmortem examination, were treated with a high dosage (8-16 g/day) of cotrimoxazole given orally together with 4 mg/kg/day of pentamidine isethionate given either intravenously or intramuscularly. Two of the patients were treated with 600 mg/day of pentamidine isethionate by inhalation and intravenous corticosteroid adjunctively.

Results

Ten patients met the criteria for inclusion in this study. There were 7 males and 3 females, with ages ranging from 32 to 78. Four patients had an underlying hematological disorder, 2 had renal disease, 2 had collagen disease, 1 had lung cancer, and 1 had sarcoidosis.

Table 3 Therapy and outcome

Patient	Other opportunistic organism	Therapy	Adverse reaction	Intravenous Corticosteroid therapy	Mechanical ventilation	Outcome of PCP
1	(−)	Cotrimoxazole (po) Pentamidine (im)	(−)	(−)	(−)	poor
2	(−)	Cotrimoxazole (po) Pentamidine (im)	(−)	(−)	(−)	poor
3	(−)	Cotrimoxazole (po) Pentamidine (im)	hypoglycemia hypotension	(−)	(−)	poor
4	(−)	Cotrimoxazole (po) Pentamidine (im)	(−)	(−)	(−)	well
5	*Haemophilus influenzae*	Cotrimoxazole (po) Pentamidine (im)	(−)	(−)	(−)	poor
6	*Candida albicans*	Cotrimoxazole (po) Pentamidine (iv, aer)	thrombopenia liver dysfunction	(+)	(+)	well
7	*Candida albicans*	Cotrimoxazole (po) Pentamidine (iv, aer)	(−)	(+)	(+)	well
8	(−)	Cotrimoxazole (po) Pentamidine (iv)	(−)	(−)	(+)	poor
9	Aspergillus spp. Cytomegalovirus	Cotrimoxazole (po)	(−)	(−)	(−)	poor
10	*Candida albicans* Cytomegalovirus	(−)	(−)	(−)	(−)	poor

*aer: aerolized, im: intramusculaly, iv: intravenously, po: per oral

All patients had received immunosuppressive therapy, such as corticosteroids. Eight patients, all but the two with adult T cell leukemia, had received the therapy for more than 2 months (Table 1). Three cases were asymptomatic when chest radiography revealed an abnormal shadow, and 5 patients had a rapid progression of cough, dyspnea, and fever, over 2-3 days. The patients with adult T cell leukemia had longer prodromes (Table 1).

The mean $P(A\text{-}a)O_2$ gradient at presentation was 69.3±23.4 torr, and the mean LDH value at presentation was 1,030±347 IU/L. To assess whether the elevated LDH values were a result of the infection or reflected other aspects of the status of the patients, we reviewed measurements prior to the acute illness. Previous values, determined 1-2 months before the diagnosis of PCP, were available in 9 patients, Comparison of these values with those at the time of diagnosis of PCP showed that all 9 patients had an increased in LDH values of more than 190 IU/L, with a median increase of 610±391 IU/L (Table 2). At the time of presentation, chest radiography revealed a bilateral reticular shadow in 5 patients, a bilateral reticular shadow and infiltrates in 4, and an AIDS-like diffuse ground glass shadow in 1 (Table 2). Two patients had *Pneumocystis carinii* cysts demonstrated at postmortem examination, but in all other patients diagnostic material was obtained while alive by TBLB and/or BAL (Table 2).

Coexisting pulmonary infections were diagnosed in 5 patients. *Candida albicans* was recognized in 3 patients, Cytomegalovirus in 2, *Haemophilus influenzae* in 1, and *Aspergillus* spp. in 1 (Table 3). Nine patients received treatment with a high dosage of cotrimoxazole and pentamidine isethionate. In 3 patients, mechanical ventilation was also used, and in 2 of these, intravenous corticosteroid and aerozolized pentamidine were prescribed adjunctively. Six patients died of progressive pneumonia. Although the other 3 patients recovered from

PCP, they died subsequently due to underlying hematological malignancy, heart failure, and multi organ failure (Table 3).

Discussion

PCP associated with AIDS often presents in an indolent fashion, with symptoms manifest for several weeks prior to presentation. Non-AIDS PCP has a more acute onset, with pulmonary symptoms progressing rapidly to respiratory failure within 1 week (Macfarlane and Finch, 1985; Engelberg *et al.*, 1984). In the present study, all patients were PCP cases from conventionally caused immunosuppression, and 8 patients had a rapid progression of symptoms for less than 2-3 days, with the patients with adult T cell leukemia having longer prodromes. In one study, patients with hematological disorders had variable prodromes ranging from 2 days to 4 weeks, which is in accordance with our results (Carter *et al.*, 1988).

Recent studies have suggested that the serum LDH value and $P(A-a)O_2$ gradient have diagnostic and prognostic implications in patients with PCP associated with AIDS (Garay and Greene, 1989). The serum LDH value is elevated in most AIDS patients when PCP is present, and usually increases with the development of the infection and decreases again with recovery, although the mechanism for this change is unknown. An association between the LDH value and survial from PCP was also noted, with survivors having significantly lower mean serum levels than those who died (El-sadr and Simberkoff, 1988). Higher values of LDH appeared to reflect more extensive interstitial inflamation. A reduction in the diffusing capacity for carbon monoxide is one of the characteristic abnormalities of pulmonary function in patients with PCP, which causes alveolar-capillary block. This abnormality is attributable to thickening of the alveolar-capillary membrane by attachment of this parasite to the epithelial surface (Sankary *et al.*, 1988). The mechanism of the increased $P(A-a)O_2$ gradient has not been fully mentioned. In our study, the LDH value and $P(A-a)O_2$ gradient at presentation were significantly elevated, and there was an increase in the LDH value at presentation over the previous values. Therefore the elevated LDH values appeared to be a result of PCP. When the patients with good outcome of PCP were compared with those with failure, the mean LDH value was 969 ± 287 vs. $1{,}000\pm392$ IU/L, and the mean $P(A-a)O_2$ gradient was 62.0 ± 9.48 vs. 74.1 ± 28.2 Torr. However there was no significant difference between the two groups. The extremly high degree of the elevation in the LDH value and the increase in $P(A-a)O_2$ gradient appeared to reflect the severity of the disease, which might account for the poor outcome in our study group. In the present study, we conclude that these values might be useful as markers for diagnosis of PCP in non-AIDS patients also.

PCP usually presents on chest radiograph as a diffuse bilateral, progressively coalescing pneumonia that in its earliest stages often spares the peripheral lung fields. PCP presenting as a pulmonary nodule or a cavity is rare, and mediastinal lymphadenopathy and pleural effusion are not believed to occur with this infection (Barrio *et al.*, 1986). In our study, chest radiography revealed a typical diffuse bilateral, progressively coalescing pneumonia, and in 5 patients bilateral diffuse infiltrates were already visible at presentation. This might suggest an acute onset of the disease in our population and the difficulty in making an early diagnosis.

It is necessary for the adequate management of PCP to obtain a definitive diagnosis at an early stage. Non-invasive methods, such as sputum induction with the use of nebulised hypertonic saline, are safe, but the sensitivity is relatively low (Yoshida *et al.*, 1978; Pitchenik

et al., 1986). In most studies, transthoracic needle biopsy has not been recommended because of its high incidence of complications. Open lung biopsy has been shown to be more reliable, but is highly invasive, and this method is currently of limited value and has not been used widely for the diagnosis of PCP in Japan (Pass *et al.*, 1986; Shorter *et al.*, 1988). Several studies have demonstrated that fiber optic bronchoscopy with BAL and TBLB is a safe and sensitive method for the initial diagnosis of PCP as well as other opportunistic infections (Oka *et al.*, 1985; Cordonnier *et al.*, 1985). In the present study, 7 BALs and 3 TBLBs were performed in 8 patients who were diagnosed as having PCP, with no complication. We suggest that fiber optic bronchoscopy, especially with BAL, is the most safe, sensitive, and rapid method for the initial diagnosis of PCP.

In half of the patients, coexisting pulmonary infections were recognized. In patients 6 and 7, *Candida albicans* was recognized for the first time in BAL, which was performed after recovering from PCP. In these cases, fluconazole was given for the treatment of the fungi, but it was supposed that prophylactic therapy might have prevented this infection. In PCP cases in the immunocompromised host, great care must also be given to coexisting infections.

Pentamidine isethionate was the first drug demonstrated to have efficacy in the treatment of PCP. Experience in immunocompromised patients demonstrated about 70% efficacy, but with substantial toxicity. Adverse reactions include renal failure, liver dysfunction, hypoglycemia, hyperglycemia, pain and swelling at the injection site, hematologic disturbances, hypotension, and pancreatitis (Salamone and Cunha, 1988; Pearson and Hewlett, 1985; Kluge *et al.*, 1978; Zuger *et al.*, 1986; Helmick and Green, 1985; Belehu and Naafs, 1982; Stahl-Bayliss *et al.*, 1986; Stoner, 1988; Montgomery *et al.*, 1989). Cotrimoxazole became the preferred therapy, with pentamidine an alternative, in cases of failure and for those with severe adverse reactions (Kovacs and Masur, 1988; Furio *et al.*, 1988). It has been suggested that a combination of cotrimoxazole and pentamidine is no more effective and may be harmful in the treatment of PCP. PCP in the non-AIDS population, however, is reported to be more fulminant, with greater incidence of treatment failure and fewer adverse reactions than those from AIDS (Drake *et al.*, 1985; Salamone and Cunha, 1988; Pearson and Hewlett, 1985; Kluge *et al.*, 1978; Kovacs *et al.*, 1984; Sattler *et al.*, 1988). It therefore seems to be useful to examine the efficacy and the incidence of adverse reactions in the concomitant use of pentamidine and cotrimoxazole in the non-AIDS population. PCP cases with acute onset tend to progress to hypoxemic respiratory failure requiring mechanical ventilation. The mortality rate for these patients is significantly high, despite optimal medical management. Several studies have demonstrated a possible role of intravenous corticosteroids in adjunctive therapy in cases with acute life-threatening respiratory failure secondary to PCP. It was also speculated in some studies that adjunctive corticosteroid therapy might obviate the use of mechanical ventilation (Gallacher *et al.*, 1989). The outcome of patients with corticosteroid therapy and the role of mechanical ventilation have yet to be examined. In the present study, pentamidine together with cotrimoxazole was prescribed for 9 patients. Although one patient showed thrombocytopenia and liver dysfunction and one other showed hypotension and hypoglycemia, seven patients sustained mild adverse reactions from the therapy and tolerated it well. Three of the 9 patients given this treatment recovered from PCP, which is a relatively poor outcome. This might be due to the severity of the underlying diseases and failure in making an ealier diagnosis. The concomitant use of pentamidine and cotrimoxazole in our study seemed no more harmful, but no more effective, than therapy with cotrimoxazole

followed by pentamidine. Two patients treated with intravenous corticosteroids and mechanical ventilation have recovered from PCP, and we suggest the possible efficacy of this regime. However, we acknowledge the low reliability of this conclusion due to the small population size and the need for evaluation in a larger patient population.

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AIDS 以外の免疫抑制患者におけるニューモシスチスカリニ肺炎の管理

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AIDS 以外の免疫抑制状態に，ニューモシスチスカリニ肺炎を発症した，10症例に臨床的検討を加えた。発症様式では，成人T細胞白血病の 2 例は前駆症状が長かったが，他の症例では急性の発症を示した。発症時の胸部レントゲンでは，全例において両側びまん性の陰影を認めた。確定診断は，8 例において経気管支的肺生検，または気管支肺胞洗浄によって，2 例において剖検によってなされた。診断時には，LDH の値は発症前の値に比べて高度に上昇しており，肺胞気動脈血酸素分圧較差も高度に開大しており，これらの値が早期診断に有用であることが示唆された。他の日和見感染の合併は，5 例に認められた。治療においては，ペンタミジンと ST 合剤の併用は，副作用は少なかったものの，有効率も低かった。コルチコステロイドは，補助療法として有用と考えられた。

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