Mod Rheumatol (2005) 15:191–197
DOI 10.1007/s10165-005-0395-9

ORIGINAL ARTICLE

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Clinical characteristics of *Pneumocystis carinii* pneumonia in patients with connective tissue diseases

Received: December 6, 2004 / Accepted: March 15, 2005

Abstract The characteristics of *Pneumocystis carinii* pneumonia (PCP) in patients with connective tissue diseases (CTDs) were examined retrospectively. Nine patients were enrolled in this study. Their mean age was 57.1 years. All the patients received a high-dose steroid or immunosuppressant. The onset (mean 6.6 days) of fever, cough, breathlessness, and geographical ground-glass opacities revealed by chest computed tomography was acute. The serum β-D-glucan level increased with a simultaneous increase in the Krebs von den Lungen (KL)-6 or surfactant protein D level. The serum immunoglobulin G (IgG) and albumin levels and the peripheral blood lymphocyte count at the onset of PCP were low, but only the serum IgG level decreased significantly. The patients were treated with trimethoprim-sulfamethoxazole or pentamidine isetionate. Six patients died eventually: two patients of progressive respiratory failure, two probably due to a recurrence of the PCP, and two with microbial respiratory infections other than PCP. Five of the six patients required mechanical ventilation. Three patients received secondary prophylaxis and survived. In conclusion, the acute onset was characteristic of PCP in patients with CTDs. High-dose steroids, immunosuppressants, and hypogammaglobulinemia are risk factors; and respiratory failure requiring mechanical ventilation, severe secondary infections, and a lack of secondary prophylaxis are poor prognostic factors. Secondary prophylaxis is recommended for all of these patients.

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Key words Connective tissue diseases (CTDs) · Hypogammaglobulinemia · *Pneumocystis carinii* pneumonia (PCP) · Prognostic factors · Risk factors

Introduction

Pneumocystis carinii pneumonia (PCP) is one of the most prevalent opportunistic infections in immunocompromised hosts.[1] Genetic analyses established that *Pneumocystis carinii* (PC) is not a protozoan but a fungus.[2] Host-specific *Pneumocystis* organisms are identified in every mammalian species, and a new name, *Pneumocystis jiveroci*, is suggested for a human-specific organism.[3] The risk factor for PCP in patients infected with human immunodeficiency virus (HIV) is a CD4 lymphocyte count lower than 200 μl.[4] Poor prognostic factors include mechanical ventilation, increased lactate dehydrogenase and C-reactive protein (CRP) levels, hypoalbuminemia, hypoxemia, and a low CD4 lymphocyte count.[5–7] Patients with connective tissue diseases (CTDs) are also at high risk for PCP.[8] PCP has been documented in patients receiving immunosuppressive therapy for systemic lupus erythematosus (SLE), dermatomyositis,[9,10] Wegener's granulomatosis,[11,12] and rheumatoid arthritis (RA).[13] PCP accounted for 4% of all microbial pneumonitis in patients with CTDs, and its mortality rate was 45.7%.[14] The risk factors in patients with CTDs included steroid or cytotoxic therapy, interstitial pneumonitis, or lymphocytopenia.[9–12,15,16] Primary prophylaxis for PCP was effective in patients with CTDs receiving steroid therapy.[17]

In this study, we retrospectively analyzed the clinical characteristics, laboratory data, radiological findings, treatment courses, and outcomes of PCP in patients with CTDs to determine whether these patients have any characteristics different from those of HIV patients with PCP.

Table 1. Background characteristics of the patients with CTDs complicated by PCP

Patient No.	Sex/Age (years)	Underlying CTDs			
		Disease	Duration (years)	Organ involvement	Treatment
1	M/52	SLE	3	NP lupus	Daily PSL 20 mg, CsA 200 mg/day
2	F/37	SLE	11	NP lupus, NS	Daily PSL 1.2 mg/kg bw, mPSL pulse[a] × 3
3	F/69	SjS, MPA	0.3	MM, IP (inactive)	Daily betamethasone 8.5 mg, betamethasone pulse[b] × 1
4	M/69	RP	0.1	Chondritis	Daily PSL 1.2 mg/kg bw
5	F/68	SjS, MPA	13	IP (inactive), GN	Daily PSL 1.2 mg/kg bw, mPSL pulse[a] × 3
6	M/72	RA	1	Pleuritis	Daily PSL 1.2 mg/kg bw, mPSL pulse[a] × 3, CPA pulse[c]
7	F/61	DM	3	IP (active)	Daily PSL 1.2 mg/kg bw, mPSL pulse[a] × 3, CPA pulse[c]
8	F/53	SLE, RA, SjS	14	Protein-losing enteropathy	Daily PSL 1.2 mg/kg bw, mPSL pulse[a] × 3
9	F/33	SLE, SjS	4	Arthritis, amyloidosis	Daily PSL 6 mg, weekly MTX 4 mg

CTDs, connective tissue diseases; PCP, *Pneumocystis carinii* pneumonia; M, male; F, female; SLE, systemic lupus erythematosus; SjS, Sjögren's syndrome; MPA, microscopic polyangiitis; RP, relapsing polychondritis; RA, rheumatoid arthritis; DM, dermatomyositis; NP, neuropsychiatric; NS, nephrotic syndrome; MM, mononeuritis multiplex; IP, interstitial pneumonitis; GN, glomerulonephritis; PSL, prednisolone; CsA, cyclosporine; mPSL, methylprednisolone; bw, body weight; CPA, cyclophosphamide; MTX, methotrexate

[a] Pulsed methylprednisolone (mPSL) of 1 g/day for three days

[b] Pulsed betamethasone of a dose equivalent to 1 g of mPSL for three days

[c] Pulsed cyclophosphamide of 500 mg/body weight

Patients and methods

Patients

Patients with CTDs admitted to our department from 1978 to 2003 were enrolled in this study. The diagnoses of CTDs were based on the criteria listed in several references.[18–23] PCP was confirmed when Grocott-Gomori methenamine-silver staining (PC-specific immunostaining) revealed the presence of PC in the bronchoalveolar lavage fluid (BALF) or transbronchial lung biopsy. PCP was presumed when a patient with respiratory distress and an increased serum β-D-glucan level without any other systemic fungal infection had some of the following features highly indicative of PCP: positivity for PC in the sputum or BALF determined by polymerase chain reaction (PCR) analysis, geographical ground-glass opacities revealed by chest computed tomography (CT), and a good response to PCP treatment. Patients with a confirmed or presumed diagnosis of PCP were examined in this study.

We examined the background characteristics; physical, radiological, and laboratory findings of the patients at the time of the PCP onset; the treatment courses and outcomes of PCP; and data on whether the patients received primary or secondary prophylaxis for PCP. Other bacterial, mycobacterial, viral, or fungal infections that developed during the pre-PCP to post-PCP courses were also documented.

Statistical analysis

Peripheral blood lymphocyte count, serum immunoglobulin G (IgG) level, and serum albumin level at PCP onset were compared with those at the start of high-dose steroid therapy or those during the maintenance therapy before the PCP onset. The analyses were performed using the paired *t*-test. Statistical analysis was performed using the standard software package Statview version 5.0 for Windows (Statview, Berkeley, CA, USA). $P < 0.05$ was considered significant.

Results

Background characteristics of patients with CTDs

Of 1042 admitted patients with CTDs, 9 (6 women, 3 men; mean age ± SD: 57.1 ± 14.4 years) who contracted PCP were examined in this study (Table 1). The patients neither received an organ transplant nor had HIV infection. The underlying CTDs are listed in Table 1. The disease durations of CTDs ranged from 0.1 to 14.0 years. The estimated incidences of PCP among patients with CTDs hospitalized in our department from 1978 to 2003 were as follows: 1 of 4 patients (25.0%) with relapsing polychondritis, 2 of 65 patients (3.1%) with vasculitic syndrome, 4 of 220 patients (1.8%) with SLE, 1 of 65 patients (1.5%) with myositis, and 1 of 362 patients (0.2%) with RA. Four patients with PCP had secondary Sjögren's syndrome; no patient with primary Sjögren's syndrome ($n = 130$) contracted PCP. The organs involved by the underlying CTDs are listed in Table 1. Among them, four patients had respiratory involvement: inactive interstitial pneumonitis was seen in two and active interstitial pneumonitis or pleuritis in one each. PCP was diagnosed in patient 1 during maintenance steroid and cyclosporine therapy and in patient 9 during maintenance steroid and weekly low-dose methotrexate therapy. Patients 2–8 received high-dose steroid (prednisolone) therapy equivalent to 1.2 mg/kg body weight daily; except for patient 4, they also were given intravenous pulsed steroid therapy. In patients 2–8, PCP was diagnosed after 6–16 weeks (9.7 ± 3.4 weeks) of high-dose steroid therapy. Among them, two of them had additional pulsed cyclophosphamide therapy. Pulsed intravenous steroid and cyclophosphamide therapies were repeated biweekly.

Table 2. Diagnosis, onset, and clinical characteristics of PCP in patients with CTDs

Patient No.	PCP diagnosis	Onset after high-dose steroid (weeks)	Clinical manifestations	Preexisting lung disease	Finding on auscultation	Interval from onset to diagnosis (days)
1	PCR (sputum, BALF)	During maintenance therapy	Fever, breathlessness	None	Crackle	3
2	Clinical diagnosis	8	Fever	None	Normal	7
3	Clinical diagnosis	6	General fatigue	IP	Crackle	2
4	Clinical diagnosis	8	Fever, breathlessness	None	Crackle	1
5	Cytology (BALF)	10	Symptomless	IP	Crackle	14
6	PCR (sputum)	16	Fever, breathlessness, dry cough	Pleuritis	Crackle	3
7	PCR (BALF)	12	Fever, breathlessness, dry cough	IP	Crackle	10
8	PCR (BALF)	8	Fever, breathlessness	None	Normal	12
9	Cytology (BALF, TBLB), PCR (BALF)	During weekly low-dose MTX therapy	Fever, breathlessness, dry cough	None	Normal	7

PCP, *Pneumocystis carinii* pneumonia; CTDs, connective tissue diseases; PCR, polymerase chain reaction; BALF, bronchoalveolar lavage fluid; TBLB, transbronchial lung biopsy; MTX, methotrexate; IP, interstitial pneumonitis

Table 3. Laboratory data at the PCP onset

Patient No.	WBC (/μl) [3700–9000]	LDH (IU/l) [120–220]	β-D-glucan (ng/l) [<20]	KL-6 (U/ml) [<550]	SP-D (ng/l) [<110]	CRP (mg/dl) [<0.3]	ESR (mm/h) [<20]	Pa_{O2} (room air) (mmHg) [85–90]
1	2000	1538	471	NA	NA	8.8	80	61
2	7800	370	149	3015	545	14.6	92	64
3	14500	774	21030	1588	781	0.5	25	27
4	7800	328	126	1487	193	14.8	84	55
5	7700	392	857	1528	136	1.2	59	80
6	12900	666	201	978	NA	19.0	120	56
7	6500	315	178	2667	265	0.2	24	64
8	9700	516	114	459	257	6.0	76	78
9	7400	540	1330	3766	256	13.2	76	60

PCP, *Pneumocystis carinii* pneumonia; WBC, white blood cell; LDH, lactate dehydrogenase; KL-6, Krebs von den Lungen-6; NA, not available; SP-D, surfactant protein D; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Pa_{O2}, arterial oxygen partial pressure
Numbers in brackets are the normal range

None of patients 1–6 or patient 9 had primary prophylaxis for PCP; patients 7 and 8 started receiving daily doses of 80 mg of trimethoprim (TMP) and 400 mg of sulfamethoxazole (SMX) after 4 weeks of high-dose steroid therapy.

Diagnosis and onset of PCP

Patients 5 and 9 had a confirmed diagnosis of PCP on the basis of the cytological test, and the remaining seven patients had a presumed diagnosis of PCP (Table 2). In four of the seven patients with the presumed PCP diagnosis, PC was detected by PCR analysis. In patients 2 to 4, the test for PC in the sputum or BALF could not be completely performed owing to serious respiratory distress. In patients 2–5, PCP developed between January and June 2000 and in patients 6–8 between February and June 2001. None of these patients was hospitalized in the same room simultaneously with one another.

Symptoms and signs

At the PCP onset, seven of the patients had fever, six had breathlessness, and three had a cough (Table 2). Patient 3 had only general fatigue, and patient 5 was completely asymptomatic. Crackles were audible on auscultation in three of the six patients without preexisting interstitial pneumonitis. PCP was diagnosed 1–14 days (mean ± SD: 6.6 ± 4.7 days) after the onset of symptoms or signs.

Laboratory data

Laboratory data at the PCP onset are listed in Table 3. The LDH and β-D-glucan levels increased in all patients, and the KL-6 and surfactant protein D (SP-D) levels also increased in all but one patient for whom data were available. The changes in β-D-glucan, KL-6, and SP-D levels are shown in Table 4 for the patients with available data. In the patients with inactive interstitial pneumonitis or without interstitial pneumonitis, the β-D-glucan, KL-6, and SP-D levels increased after the PCP onset compared with those before PCP onset. The CRP level and erythrocyte sedimentation

Table 4. Changes in β-D-glucan and KL-6 or SP-D levels

Patient No./Underlying IP	Before PCP development	At PCP diagnosis	After PCP diagnosis[a]
	β-D-glucan, KL-6, SP-D (ng/l, U/ml, ng/l)	β-D-glucan, KL-6, SP-D (ng/l, U/ml, ng/l)	β-D-glucan, KL-6, SP-D (ng/l, U/ml, ng/l)
3/Inactive	7.4, 281, 57.9	21030, 1588, 781	NA, NA, NA
4/None	4.3, 643, 19.4	126, 1487, 193	23, 2231, 110
5/Inactive	NA, 402, 17.2	857, 1528, 136	91, 1950, 38
6/None	19, 414, NA	201, 978, NA	537, 5170, NA
7/Active	18, 4719, 129	178, 2667, 265	82, 3672, 157
9/None	10.1, NA, NA	1330, 3766, 256	234, 1509, NA

IP, interstitial pneumonitis; PCP, *Pneumocystis carinii* pneumonia; NA, not available
[a] Representative data from one to four weeks after PCP diagnosis are shown

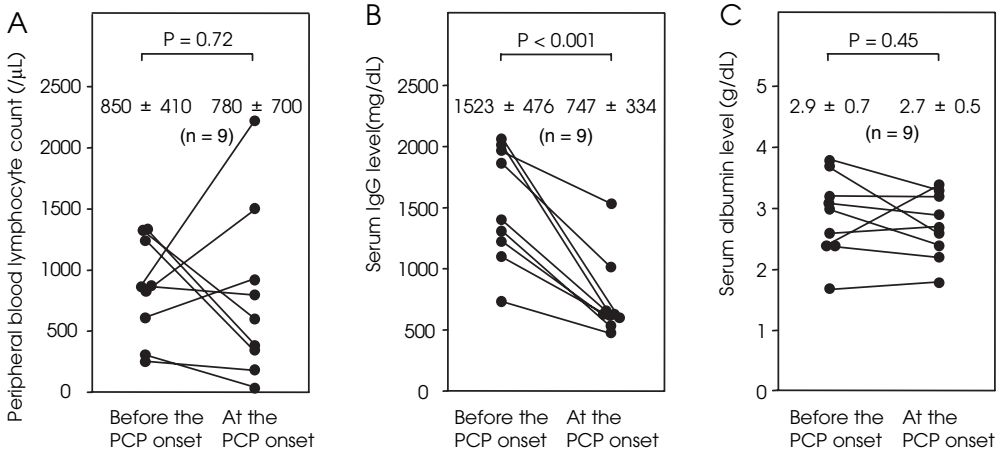

Fig. 1. Comparison of peripheral blood lymphocyte count (**A**), serum immunoglobulin G (IgG) level (**B**), and serum albumin level (**C**) before and at the onset of *Pneumocystis carinii* pneumonia (PCP). The serum IgG level decreased significantly ($P < 0.001$), but there were no significant changes in the peripheral blood lymphocyte count or the serum albumin level ($P = 0.72$ and 0.45, respectively). Values represent the mean ± standard deviation

rate was almost normal in two patients, but they increased during treatment for PCP. The partial pressures of arterial blood oxygen ranged from 27 to 80 mmHg (median 64 mmHg). Lymphocytopenia with a count lower than 1000/μl was observed in seven patients, a decreased serum IgG level in seven, and a decreased serum albumin level in nine at the time of PCP onset; the two youngest patients (in their thirties) had the lowest lymphocyte counts (39 and 190/μl, respectively). When we compared the above factors with those at the start of the high-dose steroid therapy or those during the maintenance therapy before the PCP onset, the serum IgG level had decreased significantly, although the peripheral blood lymphocyte count and serum albumin level did not show a significant change (Fig. 1).

Radiological findings

Eight patients, except patient 7, had newly developed diffuse ground-glass opacities with geographical or mosaic patterns, as revealed by chest CT. Thickened septal lines and reticular shadows were also revealed in four patients, linear shadows in two, and a nodular shadow, consolidation on air bronchograms, and pleural effusion in one. Ground-glass opacities were predominantly observed in the lower lung fields in five patients and were unilaterally distributed in two.

Treatment course and outcome

The treatment courses and outcomes are summarized in Table 5. Initially, TMP 20 mg/kg/day and SMX 100 mg/kg/day were administered orally or intravenously to all the patients. However, the antibiotics were replaced with intravenous pentamidine isethionate (PI) 4 mg/kg body weight administered daily to all but one patient because of hyperkalemia, nephropathy, rash, nausea, or cytopenia. Three of these eight patients also had adverse reactions to PI that included nephropathy, rash, cytopenia, nausea, and hypo- or hyperglycosemia. Because patient 7 had severe nausea as an adverse reaction to both oral TMP-SMX and intravenous PI, she received a daily inhalation of 300 mg of PI. Either TMP-SMX or PI was administered for at least 2–3 weeks in all the patients. Adjunctive steroid was administered in five patients.

Seven of the nine patients responded to the PCP treatment initially, but two patients had progressive respiratory failure despite the TMP-SMX or PI treatment. Six patients died eventually, all of whom had complicated bacterial infections. Two had cytomegalovirus antigenemia, and

Table 5. Treatment and outcomes of patients with CTDs complicated by PCP

Patient No.	Treatment	Mechanical ventilation	Secondary infection	Response to the PCP treatment and eventual outcome	Interval from the PCP onset to death (days)
1	TMP-SMX, mPSL pulse	+	Aspergillosis, sepsis (MRSA) CMV antigenemia	Responded, but died of disseminated aspergillosis	20
2	TMP-SMX, PI	+	Cellulitis, cystitis (*Klebsiella oxytoca*)	Responded, but died of respiratory failure with reincrease in β-D-glucan level	38
3	TMP-SMX, PI	+	Bacterial pneumonitis, sepsis (*Enterococcus* sp.)	Did not respond, died of progressive respiratory failure	10
4	TMP-SMX, PI, mPSL pulse	−	Bacterial pneumonitis (MRSA, *Pseudomonas aeruginosa*)	Responded, but died of bacterial pneumonia	59
5	TMP-SMX, PI, mPSL pulse	+	Bacterial pneumonitis, parotiditis, stomatitis (*Candida albicans*)	Responded, but died of respiratory failure with reincrease in β-D-glucan level	38
6	TMP-SMX, PI, mPSL pulse	+	CMV antigenemia, bacterial pneumonitis	Did not respond, died of DIC and gastrointestinal bleeding	20
7	TMP-SMX, PI, inhaled PI	−	None	Responded and survived after receiving secondary prophylaxis	−
8	TMP-SMX, PI	−	None	Responded and survived after receiving secondary prophylaxis	−
9	TMP-SMX, PI, daily mPSL 0.8 mg-kg bw	−	Herpes labialis	Responded and survived after receiving secondary prophylaxis	−

PCP, *Pneumocystis carinii* pneumonia; CTDs, connective tissue diseases; TMP, trimethoprim; SMX, sulfamethoxazole; mPSL, methylprednisolone; PI, pentamidine isethionate; bw, body weight; MRSA, methicillin-resistant *Staphylococcus aureus*; CMV, cytomegalovirus; DIC, disseminated intravascular coagulation

one had disseminated aspergillosis. Two patients died of respiratory failure not responding to PCP treatment, two had recurrence of respiratory failure associated with a reincreased β-D-glucan level after the discontinuation of PCP treatment, one had bacterial pneumonia, and one had disseminated aspergillosis.

Among the six patients, five required mechanical ventilation during the PCP treatment. The durations from the PCP onset to death ranged from 10 to 59 days (mean 30.8 days). Patients 7–9 received secondary prophylaxis with 80 mg of TMP and 400 mg of SMX daily, or they were given inhalation therapy of 300 mg of PI monthly following the initial treatment dose. They had neither a relapse nor severe secondary infections and recovered completely.

Discussion

In the present study, high-dose steroids, immunosuppressants, and hypogammaglobulinemia appeared to be the risk factors for PCP in patients with CTDs. PCP developed after 6–16 weeks of high-dose steroid therapy, suggesting that the patients became sufficiently immunocompromised to be susceptible to PCP within this period. In addition, a dose of 1 g of pulsed methylprednisolone may also be responsible for induction of the immunocompromised state of the hosts.[24]

Lymphocytopenia has been described as the most important risk factor for PCP.[11,15,16] However, in our series, the lymphocyte count at the onset of PCP did not significantly differ from the counts before the onset of PCP, although two patients in their thirties had severe lymphocytopenia (lymphocyte count $<200/\mu l$) and five patients had a lymphocyte count $<1000/\mu l$ at the onset of PCP. Conversely, the lymphocyte counts increased at the PCP onset in three of the nine patients. This increase was probably due to the improvement of the underlying CTDs. In these patients, the functional impairment of lymphocytes due to immunosuppressive treatment, including impaired cellular responses and interferon-γ production in response to PC may be associated with PCP development.[25] Whether a low lymphocyte count itself is a risk factor for PCP and lymphocyte function is impaired in CTD patients who contracted PCP should be further examined with a larger number of patients.

In contrast to the increased lymphocyte count, the serum IgG level decreased significantly. The decrease may be a consequence of high-dose steroid or immunosuppressant therapy. Consistent with our results, Saito et al.[26] reported that patients with PCP associated with CTDs have significantly lower IgG levels than do patients without PCP. In HIV-infected patients, the antibody level to PC decreases at the onset of PCP and returns to normal coinciding with treatment and clinical recovery from the PC infection.[27] Moreover, PCP has been documented among children with hypogammaglobulinemia.[28] These findings suggest that hypogammaglobulinemia is not merely a coincidental event of immunosuppressive therapy but is a risk factor for PCP.

Most patients had increased levels of both β-D-glucan and KL-6 or SP-D. An increased β-D-glucan level is a diag-

nostic indicator of fungal infections such as *Aspergillus*, *Candida*, and PC infections.[29] An increase in the KL-6 or SP-D level has been reported in PCP patients[30,31] but not in patients with other fungal infections. At present, PC appears to be the only pathogenic fungus that causes an increase in both β-D-glucan and KL-6 or SP-D levels. An increase in the KL-6 or SP-D level may reflect damaged alveolar epithelium in patients with PCP. We suggest that a simultaneous increase in β-D-glucan and KL-6 or SP-D levels is a diagnostic indicator of PCP in patients with inactive interstitial pneumonitis or without interstitial pneumonitis, and that it may be useful in the differential diagnosis of exacerbation of interstitial pneumonitis due to the underlying CTDs.

Primary prophylaxis for PCP using TMP-SMX has been successful in HIV patients with a CD4 lymphocyte count $<200/\mu l^9$ and in CTD patients receiving steroid therapy who had interstitial pneumonitis or lymphocytopenia.[17] Routine primary prophylaxis was not introduced until February 2001 in our department because the incidence of PCP had been extremely low. Since the latter half of 2001, however, we have prescribed 80 mg of TMP and 400 mg of SMX daily for PCP prophylaxis to patients older than 50 years at the start of high-dose steroid or immunosuppressant therapy. As none of them have had PCP to date (October 2004), it appears that primary prophylaxis for PCP is effective in patients with CTDs receiving high-dose steroid therapy.

Our observation of two clusters of PCP cases suggests exogenous transmission rather than reactivation of the latent PC infection. In such cases, PC was probably transmitted via environmental sources or the medical staff because none of our patients had direct contact with each other. Gerrard described nosocomial transmission from HIV patients to patients without HIV infection.[32] A PC genome analysis can elucidate the mode of such transmission.[33] The acute PCP onset in the present patients characteristically differs from the insidious onset in HIV patients, which takes place over several months.[34] On the other hand, the symptoms, signs, and chest CT findings in this study are all similar to those observed in HIV patients.[35]

Seven of the nine patients responded to PCP treatment initially, although six of the seven patients died eventually. The mortality rate was 67%. Ewig et al.[36] reported that a significantly higher mortality rate was associated with PCP in the non-HIV group, particularly for patients with malignancy or CTDs, than that for the HIV group. The deaths in their study were due to treatment failure and bacterial or cytomegalovirus infections. In our study, the causes associated with death were as follows: severe respiratory failure not responding to PCP treatment in two patients, respiratory failure associated with a reincreased β-D-glucan level after discontinuation of PCP treatment in two, and severe secondary infections in two. In the patients with respiratory failure associated with a reincreased β-D-glucan level, PCP recurrence was suspected because they had no findings of any fungal infections other than PC. These patients did not receive secondary prophylaxis, whereas the patients who did survive had received secondary prophylaxis. A poor prognosis is forecast for patients with respiratory failure requiring mechanical ventilation, a severe secondary infection(s), and no secondary prophylaxis. Although its standard regimen and duration, as well as its validity, have not been confirmed, we recommend secondary prophylaxis with careful monitoring of adverse reactions to TMP-SMX or PI.

Conclusions

High-dose steroids, immunosuppressants, and hypogammaglobulinemia are risk factors for PCP in patients with CTDs. The serum IgG level decreased significantly at the onset of PCP. The lymphocyte count at the onset was low, but its decrease was not significant. The acute onset was characteristic of PCP patients with CTDs, whereas other features were almost consistent with those of PCP in HIV patients. A simultaneous increase in both β-D-glucan and KL-6 or SP-D levels is a diagnostic indicator of PCP. Respiratory failure requiring mechanical ventilation, severe secondary infections, and no secondary prophylaxis are poor prognostic factors for PCP. Secondary prophylaxis should be administered to all these patients.

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