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(1→3)-β-D glucan is a diagnostic and negative prognostic marker for *Pneumocystis carinii* pneumonia in patients with connective tissue disease

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ABSTRACT

Objective. *To assess risk factors for* P. carinii *pneumonia (PCP) and compare the outcome of survivors and nonsurvivors in patients with various connective tissue diseases (CTD).*

Methods. *A retrospective study according to medical records recent 5 years was done to recruit patients with a definite diagnosis of PCP with CTD.*

Results. *Fifteen PCP patients were recruited, 10 women and 5 men (mean age: 54.4 ± 4.69 years). Positive cases of (1→3)-β-D-glucan (β-glucan) were 13 cases out of 15 (86.7%). There was a significant difference between survivors and nonsurvivors in hypoalbuminemia (p = 0.02), and high levels of β-glucan (p = 0.04).*

Conclusion. *These results suggested β-glucan could be a diagnostic and negative prognostic marker of PCP.*

Introduction

PCP is one of the most serious infections with immunocompromised hosts (1), such as acquired immunodeficiency syndrome (AIDS), malignancies, organ transplantation, and CTD. We focused on CTD, which needs steroids and/or immunosuppressants. Several studies have investigated the risk factors and incidence of PCP in patients with CTD. These reports suggested the risk factors of PCP were peripheral lymphopenia (2-5), hypoalbuminemia (3), preceding interstitial pulmonary fibrosis (5), use of high dose of steroids (2) and/or immunosuppressants (2,4). And some reports revealed that β-glucan, one of the major components of the cyst wall of *P. carinii* (6, 7), was a diagnostic marker of PCP (8, 9, 10).

Materials and methods

Fifteen patients with CTD were recruited from patients at the rheumatology division of our hospital from 1997 to 2002, about 8000 CTD outpatients per year, based on the following criteria: patients were (1) acute respiratory failure with hypoxemia, (2) recognized interstitial pneumonia with CT, (3) positive for *P. carinii* cysts by Grocott-Gomori methenamine-silver stain (Grocott stain) with bronchoalveolar lavage (BAL) fluids and/or positive for *P. carinii* by polymerase chain reaction (PCR) method with BAL fluids or sputa. PCP by PCR was performed with the method, which is well established by Wakefield *et al.* (9). Severe lymphopenia cases (less than 200/μl) were checked of HIV infection, all of them were negative of HIV. β-glucan was measured with G test (Seikagaku Corporation, Tokyo Japan) (8). This β- glucan kit was quantitative serological marker of PCP (9,10). Values > 20 pg/ml are regarded as positive (8).

Results

PCP was found in 15 patients (10 women, 5 men) who were diagnosed with RA(n = 5), SLE (n = 3), dermatomyositis (DM) (n = 3), polyarteritis nodosa (PN) (n= 2), polymyositis (PM) and systemic sclerosis (SSc) (n =1) and Sjögren's syndrome (SS) (n=1). The mean age was 54.4±18.1 years old. PCP patients were diagnosed with 14 cases by positive PCR, 2 cases positive with Grocott stain. Nine patients had preceding interstitial pneumonia and only one patient had diabetes mellitus. Initial daily doses of oral steroids were 5.0 to 60.0 mg in prednisone-equivalent, 8 patients had also immunosuppressive agents, 2 methotrexate (MTX), 2 cyclosporine (CYA), 2 azathioprine (AZP), 2 cyclophosphamide (CP). The last values of peripheral lymphocyte assessed before PCP onset were 88 to 3103/μl, serum albumin were 2.4 to 4.0 g/dl, and β-glucan were 6 to 453 pg/ml. Positive cases of β- glucan were 13 out of 15, with a sensitivity of 86.7%.

All patients were treated with full dose trimethoprim-surfamethoxazole (TMP/SMX), no patients had received prophylaxis administration of TMP/ SMX. Five patients died (global mortality: 33%). The results of multiple meta-analysis between survivors and nonsurvivors were summarized in Table I. For comparison between the group of patients of survivors and nonsurvivors, the Wilcoxon test was used. P value < 0.05 was considered significant. Lymphocytes count and CD4 count difference was not statistically significant. On the other side, there was a significant difference between survivors and nonsurvivors in hypoalbuminemia (p =

0.02), and high levels of β-glucan (p = 0.04) as shown in Figure 1 and Figure 2.

Discussion

This study, high levels of β-glucan and low levels of albumin are negative prognostic markers of poor prognosis of PCPin CTD. In general, hypoalbuminemia is one of the major risk factors of serious infection, including PCP (3). We revealed β-glucan should not only a diagnostic marker but also a negative prognostic marker for the first time.

The PCP in HIV developed by lymphopenia, specific of CD4 lymphopenia. Steroid therapy should reduce lymphocyte counts as well as their function. In fact, our study showed two PCP cases in five nonsurvivors were found without lymphopenia. Therefore risk factors of PCP with CTD should more complicated than HIV infections.

Sputum sampling is simple and noninvasive procedure for PCP diagnosis. Moreover, some reports demonstrated that the value of positive sputum samples indicated 55.5% sensitivity and a 98.6% specificity (14). Recently reported detection of *Pneumocystis carinii* DNA by PCR was significantly more sensitive than cytology; 54.5% patients were positive by PCR and only 4.5% by cytology (12).

Although TMP/SMX should most effective in prophylaxis against PCP in patients with HIV and CTD, it often causes adverse reactions for many patients including our cases. This high incidence of adverse reactions in TMP/SMX has been a limitation. However, recent randomized, double blind, controlled study reported that gradual initiation of TMP/SMX for primary PCP prophylaxis reduced the incidence of its treatment-limiting adverse effects (15).

Add that prospective studies on larger cohorts of patients are needed to confirm their results.

Table I. Charactaristics of survivors and nonsurvivors.

	Survivors n = 10	Nonsurvivors n = 5	p value	Significance
Mean age (years)	50.3 ± 19.0	62.6 ±14.7	0.11	NS
Mean lymphocyte count (μl)	1170 ±1010	766 ± 868	0.42	NS
Mean serum albumin (g/dl)	3.36 ± 0.41	2.82 ±0.33	0.02	p < 0.05
Mean serum (1→3)-β-D glucan (pg/ml)	104 ± 91.6	272 ± 135	0.04	p<0.05

Data represent mean values ± SEM.

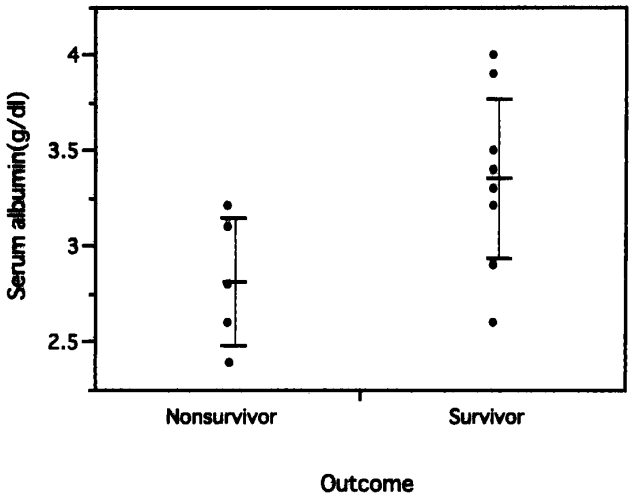

Fig. 1. Comparison of serum albumin values between 10 survivors and 5 nonsurvivors. The values with nonsurvivors (2.82 ± 0.14) is significantly lower than the values with survivors (3.36 ± 0.13). Data represent mean ± SEM. * P < 0.05.

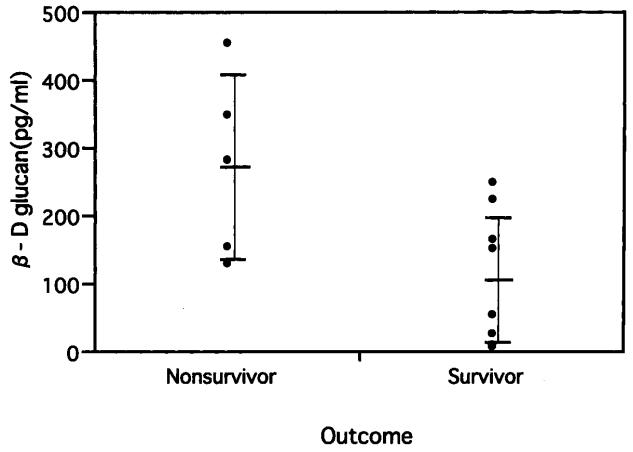

Fig. 2. Comparison of (1→3)-β-D-glucan (β-glucan) values between 10 survivors and 5 nonsurvivors. The values with nonsurvivors (272 ± 60.7) is significantly higher than the values with survivors(104 ± 28.9). Data represent mean ± SEM. * P< 0.05.

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