Pneumocystis Pneumonia in Patients with Primary Nephrotic Syndrome: Analysis of 18 Cases

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Research article

Keywords: primary nephrotic syndrome, pneumocystis pneumonia, CD4+ cell count, risk factors, outcomes

DOI: https://doi.org/10.21203/rs.3.rs-60503/v1

Abstract

Background: The aim of this study was to analysis the clinical features, risk factors and outcomes of patients with primary nephrotic syndrome (PNS) who developed pneumocystis pneumonia (PCP).

Methods: We systematically reviewed medical records from 18 PNS patients with PCP admitted to our hospital from April 2007 to April 2019. A total of 180 cases were randomly selected as controls from PNS inpatients without infection.

Results: In PCP patients, the mean age at presentation was 48.5 years, mean duration of prednisone treatment was 3.7 months and mean prednisone dose on admission was 31.3 mg/d, the most common clinical manifestation was fever (100%) and average PaO_2 on admission was 59.5 mmHg. Eight patients (44.4%) had coexisting infections, most often was cytomegalovirus (4 patients), 11 patients (61.1%) had ICU admission and 9 patients (50%) had mechanical ventilation. PCP patients had more prednisone, more immunosuppressive therapy, lower CD4+ cell counts and hemoglobin, and higher serum creatinine than those without infections ($p<0.05$). Logistic regression analysis showed that patients with prednisone usage and lower CD4+ cell counts were more likely to have PCP compared to controls ($p<0.05$). All patients survived after treatment.

Conclusion: PCP was not unusual in PNS patients, and the most important risk factor was a lower CD4+ cell count, but however, these patients had a good outcome after enough treatments.

Introduction

Pneumocystis jirovecii is a prototypical opportunistic pathogen causing an asymptomatic or mild infection in normal hosts and fulminating pneumonia (Pneumocystis pneumonia, PCP) in immunocompromised hosts [1, 2]. With the widespread use of PCP prophylaxis and highly active antiretroviral therapy, the worldwide incidence and mortality of PCP in human immunodeficiency virus (HIV) patients have declined substantially [3, 4]. Current estimates of hospital mortality for PCP in HIV patients range from 7–15% [5–7]. In contrast, PCP is being increasingly diagnosed in HIV-negative patients, in whom it carries a poorer prognosis with approximately 50% mortality [5–7].

Among HIV-negative PCP patients, studies indicate that most have hematological or solid malignancies, connective tissue diseases (CTD) or organ transplantation, and only a few patients have primary nephrotic syndrome (PNS) [8–10]. Patients with PNS have defective cell-mediated immunity, and steroid or immunosuppressive therapy causes immunologic dysfunction, which also leads to increased susceptibility to infection [11, 12]. However, the clinical characteristics for PNP patients with PCP have not been well described.

The aim of this study is to describe the clinical features, risk factors and outcomes of patients with PNS who developed PCP at a single center.

Methods

Patients

We retrospectively reviewed the medical records of PNS patients with PCP hospitalized at the First Affiliated Hospital of Wenzhou Medical University from April 2007 to April 2019. In addition, PNS patients without infection at the same time periods were randomly selected and used as controls to identify possible risk factors for the development of PCP.

PCP was defined as symptoms and radiographs compatible with PCP; confirmed by methenamine silver stain for *P. jirovecii* in the microscopic observation of samples from bronchoalveolar lavage fluid, aspirate or sputum. PNS was defined by the presence of concurrent marked proteinuria (3.5 g/day) and hypoalbuminemia (30 g/L). Patients with lupus nephritis, allergic purpura nephritis, diabetic nephropathy, amyloid nephropathy, myeloma nephropathy and other nephropathies were excluded from the review.

This study was done after agreement from the Wenzhou Medical University Research Ethics Committee and with the informed consent of all patients. This study was carried out in accordance with the declaration of Helsinki (2000) of the World Medical Association.

Data collection

Demographic, medical, and laboratory data were collected, including age and gender, PNS duration, renal pathology, duration of prednisone, prednisone dose at the time of infection, other immunosuppressive therapy over the preceding year, comorbidities, including chronic pulmonary disease, diabetes, heart disease and malignancy, interval between onset and diagnosis, fever, cough, sputum, dyspnea, arterial partial pressure of oxygen (PaO_2), laboratory data, including urine protein/24 h, serum creatinine, serum albumin, serum hemoglobin (Hb), white blood cells (WBC) and leukomonocyte, immunoglobulin G (IgG), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), CD4 + T cell count and results of chest computed tomography (CT), intensive care unit (ICU) admission, mechanical ventilation, treatments and patient outcomes.

Statistical analysis

Data was analyzed using SPSS 20 software (IBM, USA) and presented as mean ± SD, median (range), or n (%). Chi-square or Student's t-test was used to compare differences between PNS patients with PCP and PNS patients without infections, depending on which was appropriate. Binary regression logistic model was constructed to identify the risk clinical variables of PCP. We considered a 2-tailed P value < 0.05 statistically significant.

Results

Overall, 18 patients with PCP among 5400 patients with PNS in our hospital were analyzed. All PCP patients had positive methenamine silver staining and most (83.3%) had *P. jirovecii* in bronchoalveolar lavage fluid.

As shown in Table 1, the mean age at presentation was 48.5 ± 15.9 years (range: 17.8–71.2), and the female-to-male ratio was 8:10. The renal histopathologic types were membranous nephropathy in 7 patients, minimal change disease in 5 patients, and IgA nephropathy in 6 patients.The mean duration of prednisone therapy was 3.7 months, the mean prednisone dose at the time of admission was 31.3 mg/d and 14 patients (77.8%) had received other concomitant immunosuppressive therapy. The mean interval between onset and diagnosis was 5.6 days. The most common clinical manifestation was fever (100%), followed by cough (77.2%), sputum (66.7%) and dyspnea (66.7%). The average PaO_2 on admission was 59.5 mmHg. Eight patients (44.4%) had a coexisting infection, and the most common was cytomegalovirus in 4 patients.

Table 1
Clinical characters, treatments and outcomes of PNS patients with PCP (n = 18)

Variables	Patients (n = 18)
Male (n, %)	10 (55.6)
Age (years)	48.5 ± 15.9
PNS duration (months)	4.8 ± 3.9
Histological subtype	
MN (n, %)	7(38.9)
IgA nephropathy (n, %)	6(33.3)
MCD (n, %)	5(27.8)
Duration of prednisone (months)	3.7 ± 1.6
Prednisone dose at the time of admission (mg/d)	31.3 ± 9.2
Other immunosuppressive therapy	14(77.8)
CTX (n, %)	5(27.8)
MMF (n, %)	4(22.2)
Cyclosporin A (n, %)	3(16.7)
Tacrolimus (n, %)	2(11.1)
Rituximab (n, %)	0(0)
Comorbidities	7(38.9)
Diabetes (n, %)	5(27.8)
Heart disease (n, %)	2(11.1)
Chronic pulmonary disease (n, %)	1(5.5)
Malignancy (n, %)	0(0)
Interval between onset and diagnosis (days)	5.6 ± 4.2
Fever (n, %)	18(100)
Cough (n, %)	13(72.2)
Data are shown as mean ± SD, median (range), or n (%).	
PNS: primary nephrotic syndrome, PCP: pneumocystis pneumonia, MN: membranous nephropathy, MCD: minimal change disease, CTX: cyclophosphamide, MMF: mycophenolate mofetil, PaO_2: arterial partial pressure of oxygen, WBC: white blood cells, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, LDH: lactate dehydrogenase, IgG: immunoglobulin G, TMP/SMZ: trimethoprim/sulfamethoxazole, ICU: intensive care unit.	

Variables	Patients (n = 18)
Sputum (n, %)	12(66.7)
Dyspnea (n, %)	12(66.7)
PaO_2 on admission(mmHg)	59.5 ± 12.3
Coexisting infection (n, %)	8(44.4)
Cytomegalovirus (n, %)	4(22.2)
Bacteremia (n, %)	2(11.1)
Invasive aspergillosis (n, %)	1(5.6)
Mycobacterium tuberculosis (n, %)	1(5.6)
WBC(cell/mm^3)	10800 ± 3200
Leukomonocyte (cell/mm^3)	1020 ± 350
Hemoglobin (g/L)	103.8 ± 19.1
Urine protein (g/24 h)	3.1(0-10.1)
Serum creatinine (μmol/L)	112.2 ± 59.9
Albumin (g/L)	25.2 ± 4.8
ESR(mm/h)	50.1 ± 10.2
CRP(mg/L)	114.3 ± 89.9
LDH(U/L)	689.7 ± 281.2
CD4 + cell count (cells/mm^3)	281.4 ± 128.2
IgG (g/L)	5.9 ± 1.6
Radiographic findings	17(94.4)
Ground glass opacities (n, %)	
Bilateral symmetric (n, %)	15(83.3)

Data are shown as mean ± SD, median (range), or n (%).

PNS: primary nephrotic syndrome, PCP: pneumocystis pneumonia, MN: membranous nephropathy, MCD: minimal change disease, CTX: cyclophosphamide, MMF: mycophenolate mofetil, PaO_2: arterial partial pressure of oxygen, WBC: white blood cells, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, LDH: lactate dehydrogenase, IgG: immunoglobulin G, TMP/SMZ: trimethoprim/sulfamethoxazole, ICU: intensive care unit.

Variables	Patients (n = 18)
Treatments	18(100)
TMP/SMZ (n, %)	
Steroid (n, %)	12(66.7)
Caspofungin (n, %)	11(61.1)
ICU admission (n, %)	11(61.1)
Mechanical ventilation (n, %)	9(50)
Outcomes	18(100)
Survivor (n, %)	0(0)
Non-survivors (n, %)	
Data are shown as mean ± SD, median (range), or n (%).	
PNS: primary nephrotic syndrome, PCP: pneumocystis pneumonia, MN: membranous nephropathy, MCD: minimal change disease, CTX: cyclophosphamide, MMF: mycophenolate mofetil, PaO_2: arterial partial pressure of oxygen, WBC: white blood cells, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, LDH: lactate dehydrogenase, IgG: immunoglobulin G, TMP/SMZ: trimethoprim/sulfamethoxazole, ICU: intensive care unit.	

The mean CD4 + cell count was 281.4 cells/mm^3, the mean serum creatinine level was 112.2 μmol/L, and the mean LDH level was 689.7 U/L. All patients had radiographic abnormalities; 94.4% had ground glass opacities and 83.3% had bilateral symmetric opacities. Eleven patients (61.1%) were admitted to the ICU and 9 patients (50%) had mechanical ventilation.

All patients received trimethoprim/sulfamethoxazole treatment, and steroids and caspofungin were used in 66.7% and 66.1% of patients, respectively. A complete or partial remission of PCP was achieved in 14 patients (77.8%). All PNS patients with PCP survived.

180 PNS patients without PCP infection during the same period were randomly selected as controls. As shown in Table 2, PNS patients with PCP had significantly lower CD4 + cell counts and hemoglobin levels, and higher serum creatinine levels than PNS patients without PCP infection ($p < 0.001$, $p = 0.004$ and $p = 0.001$, respectively). Patients with PCP had received more prednisone and more immunosuppressive therapy (both $p < 0.001$) compared to patients without infection.

Table 2
Possible risk factors of PNS patients with PCP

Variables	PCP (n = 18)	No infection (n = 180)	P-value
Male (n, %)	10 (55.6)	108 (60)	0.803
Age (years)	48.5 ± 15.9	49.2 ± 17.3	0.760
PNS duration (months)	4.8 ± 3.9	6.7(0.1–108)	0.605
Histological subtype			0.079
MN (n, %)	7(38.9)	108(60)	
IgA nephropathy (n, %)	6(33.3)	21(11.7)	
MCD (n, %)	5(27.8)	39(21.7)	
FSGS (n, %)	0(0)	10(5.5)	
MPGN (n, %)	0(0)	2(1.1)	
Prednisone usage (n, %)	18(100)	18(10)	< 0.001
[a]Other immunosuppressive therapy (n, %)	14(77.8)	10(5.5)	< 0.001
Comorbidities			0.305
Chronic pulmonary disease (n, %)	1(5.5)	8(4.4)	
Diabetes (n, %)	5(27.8)	20(11.1)	
Heart disease (n, %)	2(11.1)	15(8.3)	
Malignancy (n, %)	0(0)	2(1.1)	
Urine protein (g/24 h)	3.1(0-10.1)	4.1 ± 2.8	0.141
Serum creatinine (μmol/L)	112.2 ± 59.9	81.2 ± 35.3	0.001
Albumin (g/L)	25.2 ± 4.8	24.9 ± 8.6	0.887
Leukomonocyte (cell/mm^3)	990 ± 350	1240 ± 420	0.033
CD4 + cell count (cells/mm^3)	281.4 ± 128.2	788.7 ± 377.2	< 0.001
Hemoglobin (g/L)	103.8 ± 19.1	121.4 ± 20.4	0.004

Data are shown as mean ± SD, median (range), or n (%).

PNS: primary nephrotic syndrome, PCP: pneumocystis pneumonia, MN: membranous nephropathy, MCD: minimal change disease, FSGS: focal segmental glomerulosclerosis, MPGN: mesangioproliferative glomerulonephritis, WBC: white blood cell, IgG: immunoglobulin G.

[a]Including cyclophosphamide, mycophenolate mofetil, cyclosporin A, tacrolimus and rituximab.

Variables	PCP (n = 18)	No infection (n = 180)	P-value
IgG (g/L)	5.9 ± 1.6	6.9 ± 2.6	0.165
Data are shown as mean ± SD, median (range), or n (%).			
PNS: primary nephrotic syndrome, PCP: pneumocystis pneumonia, MN: membranous nephropathy, MCD: minimal change disease, FSGS: focal segmental glomerulosclerosis, MPGN: mesangioproliferative glomerulonephritis, WBC: white blood cell, IgG: immunoglobulin G.			
[a]Including cyclophosphamide, mycophenolate mofetil, cyclosporin A, tacrolimus and rituximab.			

In order to identify possible risk factors of in PNS patients with PCP, we did a binary logistic regression analysis with PCP as the dependent variable (see Table 3). The results showed that patients with prednisone usage and lower CD4 + cell counts were more likely to have a PCP compared to controls (OR = 3.39, p = 0.002; OR = 0.64, p = 0.021). However, sex, age, PNS duration, histological subtype, other immunosuppressive therapy, comorbidities, and levels of leukomonocytes, hemoglobin, serum creatinine, urine protein, albumin and IgG were not included in the regression model.

Table 3

Binary logistic regression analysis with PCP as the dependent variable (R^2 = 0.702)

Variable	B	SE	P-value	OR	95% CI for OR
Prednisone usage	1.33	0.37	0.002	3.39	0.91–12.13
CD4 + cell count	-2.97	1.13	0.021	0.64	0.04–2.14
PCP: pneumocystis pneumonia, B: partial regression coefficients, SE: standard error, OR: odds ratios, CI: confidence interval.					

Discussion

Most previous studies of HIV-negative patients with PCP focused on hematological malignancies, CTD and organ transplantation. To the best of our knowledge, this is the first study about PCP in patients with PNS. Among 5400 PNS patients seen in our hospital in the past 13 years, we found 18 patients with PCP an incidence was 0.3%. Because of the low specificity of the polymerase chain reaction (PCR) for the detection of *P. jirovecii* DNA [13, 14], we excluded suspected cases with positive PCR but negative staining. Thus, the actual incidence of PCP would be higher than 0.3%. This prevalence of PCP was lower than that in patients with non-Hodgkin's lymphoma and kidney transplant, which were 0.94% and 0.91%, respectively in one study [15], but similar to that in patients with rheumatoid arthritis (0.2–0.4%) [16, 17].

In this study, we found that PNS patients with PCP were receiving a higher prednisone dose (average 31.3 mg/d) at the time of hospitalization, and 13 patients (72.2%) developed PCP around 3 to 6 months after the initiation of prednisone therapy. These findings indicated that PCP was more likely to appear 3 to 6 months after the initiation of immunosuppressive therapy, when patients did not achieve a complete

remission, and were still receiving large doses of prednisone. Findings were similar in two previous studies of PCP in HIV-negative patients [18, 19]. Also, like HIV-uninfected individuals, patients with PCP in our study typically had a rapid onset, fast progression to respiratory failure, shorter symptoms duration, higher risk of co-infections and were more likely to require ICU admission compared to HIV-infected patients [20, 21].

Although not fully characterized, the known risk factors for PCP in HIV-infected patients include underlying diseases (hematologic malignancies and CTD), use of glucocorticoids, chemotherapeutic agents, immunosuppressive agents, or monoclonal antibodies, low CD4 + cell counts and lymphopenia [22–24]. In our study, we also found that a lower CD4 + cell count was an independent risk factor for PCP. With the exception of patients with HIV, the CD4 + cell count was also a main risk factor for PCP or opportunistic infections in kidney transplant recipients and those with CTD [25, 26]. Glucocorticoids could cause rapid redistribution of lymphocytes from the circulation, depleting circulating CD4 + T cells, and to a lesser extent CD8 + T cells [27]. Different studies have demonstrated that steroid therapy increased the susceptibility to infection because of impairment of cellular immunity [28, 29].

The most important finding in our study was that all PNS patients with PCP survived and no patients died, which indicated a better outcome in these patients than in those with other conditions. Previous studies have found a higher mortality of 2 to 28% in patients with rheumatoid arthritis [30], 13 to 43% in patient with kidney transplant [31], and 30 to 60% in patients with hematological malignancies [23]. According to previous studies, possible prognostic factors in HIV-negative patients were old age, co-infections, respiratory failure, pre-existing lung disease and a higher LDH level [32–34]. The reason that no patients died in our study may be due their relatively younger age (average 48.5 years) and the disease itself. Torres et al. did a study of immunosuppressive treatment in 19 patients with membranous nephropathy and found 2 patients with PCP, both of whom survived [35]. Other investigators have also reported survival in cases of PCP infection in patients with PNS [36, 37]. In a 10-year retrospective study of 60 non-HIV Chinese children diagnosed with PCP, 2 of 8 (25%) with PNS died, while 23 of 52 (44.2%) with CTD died [38]. Wan et al. reported four patients with severe PCP and immunoglobulin A nephropathy, one of whom died [39]. These studies all indicated that PNS patients with PCP may have a better outcome than patients with other underlying conditions.

In conclusion, this study demonstrated that compared to HIV-negative patients, PNS patients had a higher incidence (0.3%) of PCP, and also had the same clinical characteristics as those with PCP. The most important risk factor was a lower CD4 + count caused by steroid or immunosuppressive therapy. However, PNS patients had a better outcome than other patients with PCP.

Declarations

Conflicts of interest

The authors have no conflicting interests that are relevant to this article.

Availability of data and materials

The datasets created during and/or analysed during the current study will be available from the corresponding author on reasonable request. There are no security, licensing, or ethical issues related to these data.

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