

A retrospective study of patients with systemic lupus erythematosus combined with *Pneumocystis jiroveci* pneumonia treated with caspofungin and trimethoprim/sulfamethoxazole

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Abstract

Systemic lupus erythematosus (SLE) complicated with *Pneumocystis jiroveci* pneumonia (PCP) is a clinical complex with unsatisfying treatment efficacy and poor prognosis which is difficult to be diagnosed at early stage. The present study aimed to investigate the clinical features of SLE with PCP, recognize the early onset indicating factors, and evaluate the treatment efficacy of combined caspofungin and trimethoprim/sulfamethoxazole (coSMZ).

We reviewed data of 9 patients admitted with SLE-PCP and treated with caspofungin combined with coSMZ at Tangshan Gongren Hospital from January 2013 to December 2017. Patients' clinical manifestation and laboratory data [leucocyte, lymphocyte, cluster of differentiation 4 (CD4)⁺T cell, lactate dehydrogenase (LDH), blood gas, etc] were compared before and after treatments. And the early onset factors of SLE-PCP, treatment efficacy of combined caspofungin and CoSMZ were analyzed.

Among these 9 patients, 8 patients suffered renal impairment, and all of them had been taking prednisone in the past 3 months at an average dose of 29.4 ± 13.6 mg/day. In addition, they had taken at least one kind of immunosuppressants. Laboratory data (leucocyte, lymphocyte, CD4⁺T cell, PaO₂, LDH) were remarkably abnormal at hospital admission, but they were improved significantly after 2 weeks of treatment, which is also statistically significant ($P < .05$), except that leukocyte had no significance change to the value at admission ($P = .973$). In addition, none of the studied patients died.

The results of the study indicated that long-term use of glucocorticoids and immunosuppressants, low CD4⁺T cell count, and renal impairment are the early-onset factors for SLE-PCP, caspofungin, when combined with CoSMZ, it could be a promising and effective strategy to treat SLE with PCP.

Abbreviations: CD4 = cluster of differentiation 4, coSMZ = trimethoprim/sulfamethoxazole, CT = computed tomography, HIV = human immunodeficiency virus, IgG = immunoglobulin G, LDH = lactate dehydrogenase, PCP = *Pneumocystis jiroveci* pneumonia, SLE = systemic lupus erythematosus.

Keywords: caspofungin, CD4⁺T cell count, *Pneumocystis jiroveci* pneumonia, systemic lupus erythematosus, trimethoprim/sulfamethoxazole

1. Introduction

Pneumocystis jiroveci pneumonia (PCP) is a common opportunistic infection in immunodeficiency population,^[1,2] especially for patients with human immunodeficiency virus (HIV).^[3] In

recent years, with the progresses of organ transplantation, tumor chemotherapy, and connective tissue disease treatment, the number of non-HIV patients infected by PCP has gradually increased,^[4] and systemic lupus erythematosus (SLE)^[4-8] is no exception. The prognosis of patients with SLE significantly improved due to large dose of hormone and immunosuppressant treatment. However, the annual infection related death rate continued to increase in patients complicated with PCP infection.^[4,9,10] At present, trimethoprim/sulfamethoxazole (coSMZ) is still the preferred medicine in the treatment of PCP. The combination of caspofungin in the treatment of PCP has been reported both in China and abroad, the prognosis of which was better than that of coSMZ alone.^[11-13] From January 2013 to December 2017, 9 patients of SLE with PCP were admitted and treated with caspofungin combined with coSMZ in Rheumatology and Immunology Department, Tangshan Gongren Hospital. The data were analyzed and reported here.

2. Methods

This study was conducted in accordance with the declaration of Helsinki and approved by the Ethics Committee of Tangshan Gongren Hospital of Hebei Medical University. It is unnecessary to yield informed consent for its retrospective character.

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Table 1**General information and use of hormones and immunosuppressants.**

No	Age	SLEDAI	Time between SLE onset and PCP diagnosis, y	Pathological type of renal puncture	Dosage of hormone in last 3 months, mg	Concurrent infections	Immunosuppressants
1	27	13	7	V	40		CTX
2	37	12	3		60		CTX
3	47	14	10	IV	55	<i>Klebsiella</i>	CTX,MTX
4	23	21	6	IV	60	<i>Klebsiella</i>	CTX,MMF
5	26	12	7		50		CTX,TAK
6	50	12	5	IV	1000	<i>Aspergillus</i>	MMF
7	45	11	4	IV+V	40		MMF
8	58	8	10	IV	1000	<i>Cytomegalovirus</i>	MMF
9	59	11	1	60			CTX

CTX=cytosan, MMF=mycophenolatemofetil, MTX=methotrexate, PCP = *Pneumocystis jiroveci* pneumonia, SLEDAI=Systemic Lupus Erythematosus Disease Activity Index, TAK=tacrolimus.

2.1. General data and application of hormone and immunosuppressants

There were 9 female patients in total, aged from 23 to 59, with an average age of 37. The onset time of these patients with SLE before the occurrence of PCP was 1 to 10 years. Among these 9 patients, 8 patients had renal impairment, and 6 patients accepted renal puncture. According to the pathological diagnosis, 4 patients went to type IV, 1 was type IV+V, and there was 1 case not typical. In the past 3 months, 7 patients accepted sufficient prednisone therapy (40–60 mg/day), 2 patients accepted 1000 mg of methylprednisolone pulse treatment (the average dose of 29.4 ± 13.6 mg/day). Within 3 months before the occurrence of PCP, these 9 patients had taken at least 1 kind of immunosuppressants. That is, cytoxin for 2 patients, cytoxin with methotrexate for 1 patient, cytoxin with mycophenolatemofetil for 1 patient, cytoxin with tacrolimus for 1 patient, and mycophenolatemofetil for the rest of the 4 patients. During the PCP infection period, all 9 patients were active in SLE, the Systemic Lupus Erythematosus Disease Activity Index score was 12.7 ± 3.5 . Furthermore, none of them had been diagnosed with pulmonary interstitial lesions before the occurrence of PCP (refer to Table 1 for general data of the 9 patients).

2.2. Clinical manifestation and laboratory examination

The time duration from the onset of symptoms to definitive diagnosis of PCP was 4 to 28 days (13.3 ± 8.7 days). All 9 patients had fever, with temperature of 38°C to 40°C, and they began to cough, the amount of white sputum was not large. After 2 to 5 days, these patients were followed by chest distress and breath

obstruction symptoms review. In addition, polypnea became obvious after exercise. No significant lung sign was, however, found upon physical examination, not in line with the manifested symptoms of these patients. In terms of laboratory examinations, 3 out of 9 patients had elevated leukocyte ($11.3\text{--}15.8 \times 10^9$), 2 patients' leukocyte decreased, and the remaining 4 patients were in the normal range, with an mean value of $8.29 \pm 4.50 \times 10^9$. The absolute value range of lymphocytes was $0.3\text{--}0.68 \times 10^9$, and mean value was $0.49 \pm 0.13 \times 10^9$, cluster of differentiation 4 (CD4)⁺T cell count was 34 to 98/ μ L, and the mean value was $59 \pm 24/\mu$ L. Plus, the PaO₂ 5.2 to 9.2 kPa and mean value was 7.7 ± 1.2 kPa. Nine patients presented significant lactate dehydrogenase (LDH) increase, the mean value was 854 ± 288 U/L. For the 9 patients, the mean value of immunoglobulin G (IgG) was 5.3 ± 2.2 g/L, significantly lower than the normal range (normal reference value: 6.8–14.5 g/L). All patients received serological HIV antibody test, and none was positive. Chest x-ray image revealed that 5 patients developed diffuse exudation in bilateral lungs, 2 had significant increased lung markings, whereas the other 2 had normal lung markings. According to the chest computed tomography (CT), all 9 patients manifested with interstitial lung disease, and diffuse ground glass shadows were found in both lungs. Among these patients, 2 were with pleural effusion (refer to Table 2 for general data of the 9 patients).

2.3. Concurrent infection

Among the 9 patients, 4 were complicated with concurrent infections, 2 patients were diagnosed with *Klebsiella pneumoniae* infection by sputum culture, 1 suffered from concurrent

Table 2**Clinical manifestation and laboratory examination of 9 patients.**

No	Length of hospital stay	Lymphocyte, $\times 10^9$ /L	CD4 ⁺ T cell count, / μ L	IgG, g/L	LDH, U/L	PO ₂ , kPa	Dosage of hormone, mg/day	Serum β -1,3-glucan, pg/mL
1	31	0.30	35	7.14	1070	7.9	20	392.5
2	18	0.60	42	8.66	297	8.6	30	53.1
3	24	0.42	69	5.25	745	8.0	25	160.4
4	28	0.47	78	2.22	980	7.6	30	378.2
5	34	0.52	36	3.56	789	7.0	20	117.6
6	38	0.49	34	5.78	1026	6.8	60	1000.0
7	26	0.30	62	2.78	978	8.9	25	530.7
8	42	0.60	79	7.80	567	5.2	45	255.8
9	25	0.68	98	4.83	1238	9.2	20	578.6

IgG=immunoglobulin G, LDH=lactate dehydrogenase.

Table 3
Comparison of indicators pre- and post-treatment (n=9).

	Blood gas		Blood routine		CD4 ⁺ T cell, / μ L	LDH, U/L
	PCO ₂ , kPa	PO ₂ , kPa	Leukocyte, $\times 10^9$ /L	Lymphocyte, $\times 10^9$ /L		
Pretreatment	4.07 \pm 0.35	7.69 \pm 1.23	8.29 \pm 4.50	0.49 \pm 0.13	59.22 \pm 23.48	854 \pm 288
Post-treatment	5.28 \pm 0.59	9.21 \pm 1.20	8.44 \pm 2.13	0.77 \pm 0.20	84.44 \pm 18.45	433 \pm 182
P	.000	.018	.927	.003	.023	.002

CD4 = cluster of differentiation 4, LDH = lactate dehydrogenase.

Aspergillus infection (galactomannan test 467 pg/mL), and the other case was with positive cytomegalovirus immunoglobulin M antibody complicated with cytomegalovirus infection (refer to Tables 1 and 2 for general data of the 9 patients).

2.4. Diagnostic criteria

The diagnosis of SLE was based on the SLE classification developed by the American Rheumatology Academy in 1997. The cysts of pneumocystis were seen in sputum by the bronchoalveolar lavage or tracheal aspiration, serum β -1,3-glucan of 9 patients elevated remarkably and the highest was 1000 pg/mL, >500 pg/mL in 4 cases (refer to Table 3).

2.5. Treatment and prognosis

Nine patients had received multiantibiotic treatment at different stages before PCP was diagnosed. However, they continued to develop fever and chest distress, breathing obstruction symptoms gradually aggravated. And according to clinical examination, 2 of them were suspected of infecting PCP. Therefore, caspofungin was initiated 2 to 3 days before the definitive diagnosis was made. Caspofungin was used in the other 7 patients when the definitive diagnosis of PCP was confirmed. And all 9 patients received coSMZ treatment, too. The first dose of caspofungin was 70 mg/day, which decreased to 50 mg/day from the 2nd day and continued for 7 to 21 days. CoSMZ was administrated 20 mg/kg of SMZ once every 6 hours, with a course of 21 days. Meanwhile, among these 9 patients, 2 received piperacillin treatment of 12 and 16 days, respectively, which were then stopped when sputum culture turned negative, and 1 received ganciclovir treatment for

14 days. All 9 patients stopped the administration of immunosuppressants during their PCP treatment, and hormone dose increased to 40 to 80 mg/day of intravenous methylprednisolone in 7 to 10 days, and gradually decreased afterwards. Three patients were transferred to ICU due to respiratory failure, one of which accepted mechanical ventilation for 6 days due to acute respiratory distress syndrome caused by severe type I respiratory failure, and at the same time, this patient complicated with *Aspergillus*, in this regard, the usage of caspofungin was prolonged to 21 days.

After the completion of the treatments above, conditions of all 9 patients were improved, and their body temperatures returned to normal within 1 to 4 days. After 3 to 7 days, their respiratory symptoms almost disappeared. About 10 days later, lung CT scan re-examination was performed for them, and it revealed that the lesions were absorbed immensely (one of the patients lung CT scan pre- and post-treatment is displayed in Figs. 1 and 2). And the changes in laboratory data after 2 weeks of treatment is as follows: mean value of leukocyte showed no significant change when compared to the value at admission ($P = .973$); mean values of lymphocyte, CD4⁺T cell, PaO₂ and PaCO₂ elevated markedly when compared to the values at admission and resulted in clinical significance ($P < .05$); mean value of LDH decreased obviously when compared to the value at admission and also resulted in clinical significance ($P < .05$) (Table 3). In addition, the average hospital-stay duration was 30 days, the shortest was 18 days, and the longest was 42 days, the 3 patients in ICU stayed in for 11, 16, and 22 days, respectively and were transferred to general ward when their conditions improved (Table 2). All of the 9 patients recovered and were discharged from the hospital. However, they still needed to continue with rational systemic treatment of SLE.



Figure 1. Lung computed tomography scan showed diffuse ground-glass opacities and interstitial lesions in bilateral lung fields before treatment.

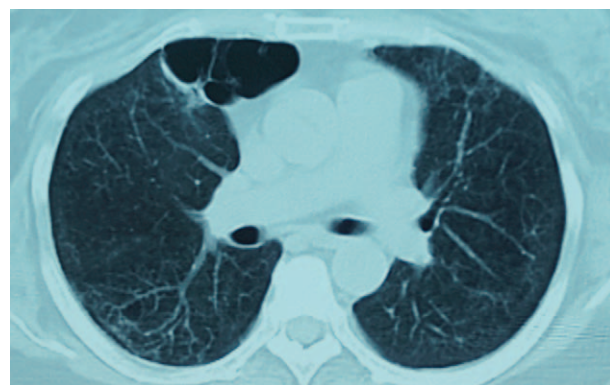


Figure 2. The lesions were absorbed immensely after 14 days of combined treatment.

3. Discussion

The study suggests that long onset time, coupled with the significantly active stage of SLE, renal involvement, and recent administration of large dose of hormone and immunosuppressants, are the hazardous factors of SLE with PCP, especially for SLE patients of low IgG and low lymphocyte anemia, which is consistent with other relevant domestic and foreign reports.^[14–16]

CoSMZ is the first-choice medication in clinical treatment of PCP. Retrospective data of 8 patients admitted in our department before 2013 showed that they were treated with coSMZ alone, and 4 of them died, mortality rate was 50%, in line with the mortality rate of the related studies.^[10,16–18] Therefore, it is particularly crucial to find a more effective method for the treatment of PCP. As for the 9 patients in this review, 2 were treated with caspofungin for anti-PCP purpose before the diagnosis was confirmed, and coSMZ was added after the diagnosis; 7 patients were treated with caspofungin combined with coSMZ immediately after the diagnosis of PCP, all 9 patients survived with good condition. Darius Armstrong-James from Imperial College, UK analyzed 80 patients with PCP retrospectively, 12 cases were treated with first-line drug coSMZ, and it is shown that the patients still tended to get worse. Although the symptoms were improved significantly after the addition of caspofungin, 10 survived and 2 died.^[12] Some Chinese doctors had also made report on the combined treatment strategy for PCP. Dr. Zhang Gensheng from Zhejiang University School of Medicine used caspofungin and coSMZ as a first-line treatment regimen for non-HIV PCP patients, and the results were similarly effective.^[13] However, the primary disease of the patients in the above studies were not SLE, this study focused on the effect of combined use of caspofungin and coSMZ in patients of SLE with PCP, and hopefully, they could serve as a supplementary report to the treatment regimen. The results of this study are similar to those of the above studies, for both of them had proven that the combination of 2 drugs is effective in the treatment of PCP. Apart from that, the mechanisms may be as follows: caspofungin may affect cyst formation by inhibiting β -glucan synthesis, whereas only exhibiting weak effects on trophic forms^[19]; similarly, coSMZ may only affect trophic forms by interfering with folate metabolism.^[20,21] Therefore, the joint use of caspofungin and coSMZ may inhibit the entire life cycle of *Pneumocystis jiroveci*. Alternatively, caspofungin may decrease β -glucan-induced excessive inflammatory responses by inhibiting β -glucan synthesis,^[22] whereby alleviating PCP.

In this study, patients' body temperatures returned to normal in 1 to 4 days after combined therapy, and respiratory symptoms subsided in 3 to 7 days. The reasons for the rapid response may be as follows: Although coSMZ takes effect slowly, requiring 5 to 8 days before it shows curative effect,^[23] caspofungin was able to respond rapidly; hence, it may be inferred that combination treatment of coSMZ and caspofungin may compensate the coSMZ deficiency occurred in patients receiving delayed PCP treatment. The combination therapy not only took effect quickly, but also showed significant changes in laboratory tests after 2 weeks of treatment. PaO₂ elevated from 7.69 ± 1.23 to 9.21 ± 1.20 kPa, CD4⁺T elevated from 59.22 ± 24.28 to 84.44 ± 18.45/μL, whereas the LDH decreased from 854 ± 288 to 433 ± 182 U/L, $P < .05$; thus, it can be seen that all of the parameters are clinically significant. In addition, the rapid improvement of these indicators not only indicates that the curative effect is remarkable, but also provides positive significance for prognosis.

The synergistic effect of the 2 plays an important role in the treatment of PCP.^[13,24]

Although the treatment regimen has not been included in the PCP guidelines, it has been recommended by experts both in China and abroad.^[10,24]

Given the low incidence of SLE with PCP and the small sample size of this study, only descriptive reports are made available here. And the effectiveness of this treatment strategy needs to be further verified by multicenter researches.

To sum up, renal impairment, active SLE, recent use of large dose of hormone, and immunosuppressants, especially low IgG and hypolipidemia, CD4⁺ T cell <90/μL, are all risk factors for patients with PCP.^[25,26] In this study, all 9 patients were cured, with no mortality, which is probably related to the combination of the 2 drugs, suggesting that this may be a promising treatment strategy for SLE patient complicated with PCP.

Author contributions

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