

Combined Caspofungin and Trimethoprim/ Sulfamethoxazole Therapy for Severe *Pneumocystis Jirovecii* Pneumonia

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Dear the Editor

Pneumocystis pneumonia (PCP) caused by *Pneumocystis jirovecii* (PJ) is a major cause of mortality and morbidity in immunocompromised patients, especially in HIV-positive persons. Trimethoprim/ sulfamethoxazole (TMP /SMZ) is first choice for drug of standard therapy or prophylaxis for PCP [1-3]. Caspofungin in combination with TMP/SMZ as salvage therapy for severe PCP was ever reported [1-4].

A 33 years old HIV-infected man was admitted to the hospital due to bilateral pneumonia with septic shock. Endotracheal intubation was performed with mechanical ventilation for acute respiratory failure on July 20, 2018.

Laboratory data revealed a total lymphocyte count of 600/ μ L, with a CD4⁺ count of 20 % and CD8⁺, 57.9 % (CD4⁺/CD8⁺ ratio, 0.05). Arterial blood gas analysis showed a PH of 7.442; PCO₂, 24.7 mmHg; PO₂, 149.0 mmHg; HCO₃⁻, 17.0 mmol/L; Base Excess, -4.4 mmol/L; and P/F ratio, 149.0 mmHg under FiO₂, 100 %. Virology survey showed an HIV viral load of 586,654 copies/ml; cytomegalovirus (CMV) viral load, 67,608 IU/mL; and positive results of polymerase chain reaction (PCR) assay for CMV in blood and sputum samples. The result of DNA PCR for PJ was positive in transbronchial aspirates, revealing wild types of Thr55Ala and Pro57Ser by PJ DNA sequencing analysis (Table 1). Sputum MTB-PCR (Gene Xpert assay) was negative. The blood and sputum cultures did not yield any bacterial growth. A chest X-ray (CXR) film showed ill-defined infiltration and haziness over both lung fields (Figure 1, Table 1).

The patient received therapy with ceftriaxone and levofloxacin for suspected bacterial infection. TMP/SMZ, methylprednisolone and








caspofungin were initiated for PCP. Ganciclovir was added for CMV DNAemia with probable pneumonitis. However, pneumonia in worsening progression (Figure 2) accompanied with leukopenia (1900/ μ L) was noted (Table 1). Then IVIG was prescribed on July 26. PJP DNA PCR remained positive on August 2, 2018, but CXR film showed substantial improvement (Figure 3, Table 1). Intravenous ganciclovir was de-escalated to oral valganciclovir. However, a new onset of fever with an elevated procalcitonin (PCT) level up to 28.37 ng/mL (normal, < 0.05) occurred and carbapenem-resistant *Acinetobacter baumannii* (CRAB) was isolated from sputum culture obtained on August 3. Then antibiotics with ceftriaxone and levofloxacin were shifted to meropenem and sulbactam in combination and subsequent colistin therapy alone. Combined therapy with TMP/SMZ and caspofungin was maintained for PCP. Nonetheless, worsening dyspnea was noted and the CXR film showed left pneumothorax, atelectasis of left lung and thus chest tube was inserted on August 9 (Figure 4, Table 1). Leukopenia got improvement after IVIG infusion therapy. Tracheostomy was performed on August 13. A followed-up CXR film showed improvement (Figure 5, Table 1), and thereby training for weaning respiratory ventilator was started since August 15.

However, distended abdomen and vomiting were noted. Gastroparesis with ileus was considered (Figure 6, Table 1). Peripheral parenteral nutrition using SmofKabiven with glutamine was given. The CXR showed improving pneumothorax, and thus chest tube was removed on August 24. As negative PJ-PCR and a CMV viral load lowering to 454 IU/mL, caspofungin was discontinued and TMP/SMZ was shifted to oral-form TMP/SMZ. Thereafter,

intravenous ganciclovir was shifted to oral valganciclovir. Patient's respiration, CXR patterns and inflammatory parameters were better. He was transferred to the ward on August 29. After medical therapy, his lung condition

was well controlled (Figure 7, Table 1) and he was then discharged on September 14, 2018. The patient has undergone regular follow up uneventfully for 3 months.

Table1. Clinical courses including laboratory data, serial X-ray films and treatment of the patient during hospitalization of this episode

Date of events	7/20	7/26	8/2	8/9	8/16	8/23	8/31
HIV viral load (copies/mL)	586,654					80	
PJ-PCR	Positive	Positive	Positive	Positive	Positive(weak)	Negative	
CMV-PCR (blood)	Positive	Positive	Positive	Positive	Positive	Positive	
CMV-PCR (sputum)	Positive	Positive	Positive	Positive	Not detected	Not detected	
CMV viral load(IU/mL)	67,608	29,601	49,310	1,776	1,203	454	
Blood / UrineCulture	No growth	No growth (7/24)	No growth (8/3)				
Sputum Culture	No growth		CRAB (8/3, 8/13) , CRAB + <i>Escherichia coli</i> (8/20)			<i>Serratiamarcescens</i> (8/28, 8/30)	
White blood cell count/ μ L	12,400	1,900	5,200	6,500	7,300	9,400	7,700 (8/27)
C-reactive protein (mg/L)	172.6	48.8	253.7 (8/4)	38.4	53.2	3.7	8.8 (8/27)
Procalcitonin (ng/mL)	13.21	0.21	28.37 (8/4)	1.12	0.25	0.05	0.05 (8/27)
X-rayimaging series	 bilateral infiltrates (Figure 1)	 worsening (Figure 2)	 improving (Figure 3)	 worsening (Figure 4)	 improving (Figure 5)	 ileus (Figure 6)	 improving (Figure 7)
Antibiotic therapy	Levofloxacin + Ceftriaxone 7/20-8/4			.Meropenem + Sulbactam8/4-8/16		Colistin (intravenous), Q6H, 8/16-8/23; Colistin (inhalation), TID, 8/24-8/31	
Anti-PCP therapy	TMP-SMZ (400mg/800mg) 3 vials Q6H+ Caspofungin 70mg (7/20), 50mg QD 7/21-8/22					TMP-SMZ(400mg/800mg) 2 #bid, PO.8/22-9/14	
Anti-CMV pneumonitis	Ganciclovir 150 mg Q12H 7/20-7/29; IVIG 2g 7/26-7/30		Valganciclovir900 mg PO 8/1-8/9; IVIG 1g 8/1-8/4; 0.5g 8/5-8/9		Ganciclovir 150 mg Q12H8/9-8/27		Valganciclovir 900mgbid28-8/31

Lobo et al. demonstrated that the efficacy of caspofungin combined with the TMP/SMZ was significantly higher than that of each drug alone [2]. This combination may inhibit the entire life cycle of *Pneumocystis jirovecii* [4], and may achieve better outcomes if it is rapidly administered to patients as a first-line therapy, particularly in those requiring invasive mechanical ventilation [2, 4]. In addition, the worsening hit of the course during August 4 to August 9 seemed due to nosocomial CRAB pneumonia and early de-escalation of intravenous ganciclovir to oral valganciclovir. These results imply that CMV might play a significant role of co-infection with PCP, further compromising the immunity of the patient and contributing to complexity and severe severity of the lung infections.

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