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Veno-Venous Extracorporeal Membrane Oxygenation for Severe *Pneumocystis jirovecii* Pneumonia in an Immunocompromised Patient without HIV Infection

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Pneumocystis jirovecii pneumonia (PJP) occurs in immunocompromised hosts and is classified as PJP with human immunodeficiency virus (HIV) infection (HIV-PJP) and PJP without HIV infection (non-HIV PJP). Non-HIV PJP rapidly progresses to respiratory failure compared with HIV-PJP possibly due to the difference in immune conditions; namely, the prognosis of non-HIV PJP is worse than that of HIV PJP. However, the diagnosis of non-HIV PJP at the early stage is difficult. Herein, we report a case of severe non-HIV PJP successfully managed with veno-venous extracorporeal membrane oxygenation (V-V ECMO). A 54-year-old woman with neuromyelitis optica was treated with oral corticosteroid, azathioprine, and methotrexate. She admitted to our hospital for fever, dry cough, and dyspnea which developed a week ago. On admission, she required endotracheal intubation and invasive ventilation for hypoxia. A chest computed tomography (CT) scan revealed ground-glass opacity and consolidation in the both lungs. Grocott staining and PCR analysis of bronchoalveolar lavage fluid indicated the presence of fungi and *Pneumocystis jirovecii*, respectively, whereas serum HIV-antibody was negative. The patient was thus diagnosed with non-HIV PJP and was treated with intravenous pentamidine and corticosteroid pulse therapy for PJP. However, hypoxia was worsened; consequently, V-V ECMO assistance was initiated on day 7. The abnormal chest CT findings and hypoxia were gradually improved. The V-V ECMO support was successfully discontinued on day 14 and mechanical ventilation was discontinued on day 15. V-V ECMO could be a useful choice for respiratory assistance in severe cases of PJP among patients without HIV infection.

Keywords: non-human immunodeficiency virus; pentamidine; *pneumocystis jirovecii* pneumonia; respiratory failure; veno-venous extracorporeal membrane oxygenation
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Introduction

Pneumocystis jirovecii pneumonia (PJP) is an infectious respiratory disease that occurs in immunocompromised hosts. PJP is clinically classified as PJP with human immunodeficiency virus (HIV) infection (HIV-PJP) and PJP without HIV infection (non-HIV PJP) because of the difference in therapeutic strategy and prognosis. Non-HIV PJP could occur in patients with immunodeficiency status without HIV infection, such as post-organ transplants, malignant diseases, and chronic inflammatory diseases under immunosuppressant therapy. The prognosis of PJP in non-HIV-infected patients is usually worse than that of PJP in HIV-infected patients (Ewig et al. 1995). PJP in non-HIV-infected patients often results in fatal respiratory failure (Liu et al. 2017). Delay in treatment from patients with

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non-HIV PJP is likely to be related to the delay in the diagnosis of PJP, for which the clinical manifestations and radiologic abnormalities are nonspecific (Li et al. 2014; Liu et al. 2017). The number of PJP cases in patients with HIV is decreasing; on the other hand, the number of PJP cases in non-HIV-infected patients is increasing in association with the increase in the number of patients receiving immunosuppressant therapy for autoimmune disease and transplantation (Maini et al. 2013). The mortality of patients with non-HIV PJP is worse than that of patients with HIV PJP (Ewig et al. 1995). Bronchoalveolar lavage (BAL) fluid in HIV PJP contains higher numbers of PJP organism which could facilitate the early diagnosis and treatment. The numbers of neutrophils are usually lower in HIV PJP compared with non-HIV PJP (Limper et al. 1989). The difference of immune status could be related to better outcome in HIV PJP. The overall mortality for patients with non-HIV PJP is approximately 30% (Liu et al. 2017). Moreover, overall mortality of patients with non-HIV PJP who are admitted to the ICU is reported to be 75.6% (Weng et al. 2016).

The veno-venous extracorporeal membrane oxygenation (V-V ECMO) machine supports the function of the lungs. A basic circuit is composed of a blood pump, a membrane lung (or oxygenator), a heat exchanger, and cannulas and tubing. In a typical circuit of V-V ECMO, venous blood is drained out of the right venae cavae via a femoral venous cannula, passed through a pump and a membrane lung for gas exchange, and oxygenated blood is then returned to the right internal jugular venous cannula (Combes et al. 2014). V-V ECMO is useful for promoting optimal gas exchange and allowing the lungs to rest in patients with respiratory failure (Yadav et al. 2017). The evidence of efficacy of V-V ECMO for severe respiratory failure is increasing (Kolla et al. 1997; Linden et al. 2000; Davies et al. 2009; Peek et al. 2009); however, it is still unknown what kind of patients with severe respiratory failure could be saved with V-V ECMO assist. Several cases of PJP in HIV-infected patients were successfully managed with V-V ECMO (Cawcutt et al. 2014; Ali et al. 2016; Mauri et al. 2016; Horikita et al. 2017; Lee et al. 2017; Morley et al. 2017; Capatos et al. 2018; Ramanathan et al. 2018). As non-HIV PJP more frequently progresses to respiratory failure compared with HIV PJP, non-HIV PJP could be the indication for V-V ECMO assistance. Little is known, however, about the efficacy of V-V ECMO for cases of PJP in patients not infected with HIV (Geelhoed et al. 1974; Wu et al. 2012; Kida et al. 2018; Russell et al. 2018). It is important to know the clinical course and prognosis of non-HIV PJP who are managed by V-V ECMO. Herein, we report a case of non-HIV PJP who were successfully managed with V-V ECMO.

Case Report

A 54-year-old women was admitted to our intensive care unit (ICU) due to fever, dry cough, and dyspnea continuing for a week. She was receiving 15 $mg \cdot day^{-1}$ of oral corticosteroid, 50 $mg \cdot day^{-1}$ of azathioprine, and 4 $mg \cdot week^{-1}$ of oral methotrexate for neuromyelitis optica. Prophylactic administration of trimethoprim/sulfamethoxazole (TMP/SMX) for PJP had been discontinued 6 months earlier with the decision of neurologist. She was a never-smoker.

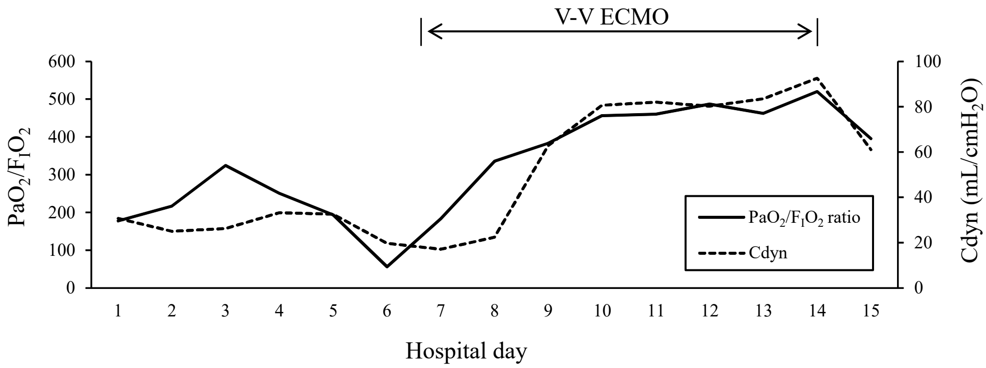
Her body temperature was 39.0°C, blood pressure 115/81 mmHg, pulse rate 126 $beats \cdot min^{-1}$, respiratory rate (RR) 30 $breaths \cdot min^{-1}$, and SpO_2 50% at room air. Her PaO_2 was 26.8 torr with 5 $L \cdot min^{-1}$ oxygen inhalation by mask. She was intubated and received mechanical ventilation on admission (mechanical ventilation setting; assist/control [A/C], pressure control, F_IO_2 1.0, RR 16 $breaths \cdot min^{-1}$, positive end-expiratory pressure [PEEP] 12 cmH_2O, and peak inspiratory pressure [PIP] 28 cmH_2O). The PaO_2/F_IO_2 ratio and dynamic compliance (Cdyn) were decreased to 177 (PaO_2 177 torr with F_IO_2 1.0) and 30.6 $mL \cdot cmH_2O^{-1}$, respectively (Fig. 1). Physical examination on admission revealed mild fine crackles in the lung fields bilaterally. Laboratory data on admission included a white blood cell count of 4,550 $cells \cdot mm^{-3}$ with 77.8% neutrophils, 15.2% lymphocytes, and 3.5% eosinophils; and C-reactive protein of 15.12 $mg \cdot dL^{-1}$. Serum β-D glucan and KL-6 levels were elevated to 577.1 $pg \cdot mL^{-1}$ and 1,023.7 $U \cdot mL^{-1}$, respectively. A chest high-resolution computed tomography (CT) scan showed ground-glass opacity and consolidation in the bilateral lung fields (Fig. 2A). Grocott staining-positive cysts were observed in the bronchoalveolar lavage (BAL) fluid (Fig. 3). Polymerase chain reaction analysis of the BAL fluid indicated the presence of *Pneumocystis jirovecii*. The serum anti-HIV antibody titer was within the normal range. We diagnosed the patient as non-HIV PJP.

We initiated methylprednisolone pulse therapy at a dose of 1 $g \cdot day^{-1}$ for 3 days, followed by prednisolone at a dose of 60 $mg \cdot day^{-1}$ and intravenous pentamidine at a dose of 3 $mg \cdot kg^{-1} \cdot day^{-1}$. Intravenous doripenem at a dose of 1.0 $g \cdot day^{-1}$ and azithromycin hydrate at a dose of 0.5 $g \cdot day^{-1}$ were also administered. The PaO_2/F_IO_2 ratio immediately improved to 324 (PaO_2 162 torr with F_IO_2 0.5), but the Cdyn decreased to 26.1 $mL \cdot cmH_2O^{-1}$ on day 3. The PaO_2/F_IO_2 ratio decreased to 250 (PaO_2 125 torr with F_IO_2 0.5) on day 4. We increased the dose of pentamidine to 4 $mg \cdot kg^{-1} \cdot day^{-1}$. Chest CT showed worsening of the ground-glass opacity and consolidation in the lung fields bilaterally on day 5 (Fig. 2B). On day 6, the PaO_2/F_IO_2 ratio and Cdyn were further decreased to 55.7 (PaO_2 55.7 torr with F_IO_2 1.0) and 19.6 $mL \cdot cmH_2O^{-1}$, respectively (mechanical ventilation setting; synchronized intermittent mandatory ventilation [SIMV], F_IO_2 1.0, RR 34 $breaths \cdot min^{-1}$, PEEP 2 cmH_2O, PIP 14 cmH_2O). The Murray score was 3.0 (chest X-ray score 4, 4 for PaO_2/F_IO_2 ratio, 0 for PEEP, 4 for compliance) (Murray et al. 1988). On day 7, V-V ECMO was started with sweep gas flow at 3 $L \cdot min^{-1}$ and blood flow at 3 $L \cdot min^{-1}$. The mechanical ventilation setting was changed

A

Hospital Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Ventilation Mode	A/C	A/C	SIMV	SIMV	SIMV	SIMV	SIMV	SIMV	SIMV	CPAP	CPAP	SIMV	SIMV	SIMV	SIMV
F_IO2	1.0	0.6	0.5	0.5	0.5	1.0	0.4	0.4	0.4	0.3	0.3	0.4	0.4	0.4	0.4
PEEP [cmH_2O]	12	12	10	10	10	2	10	10	10	10	10	10	10	10	5
PIP [cmH_2O]	28	28	26	26	26	14	16	16	12	16	16	16	16	16	16

B



C

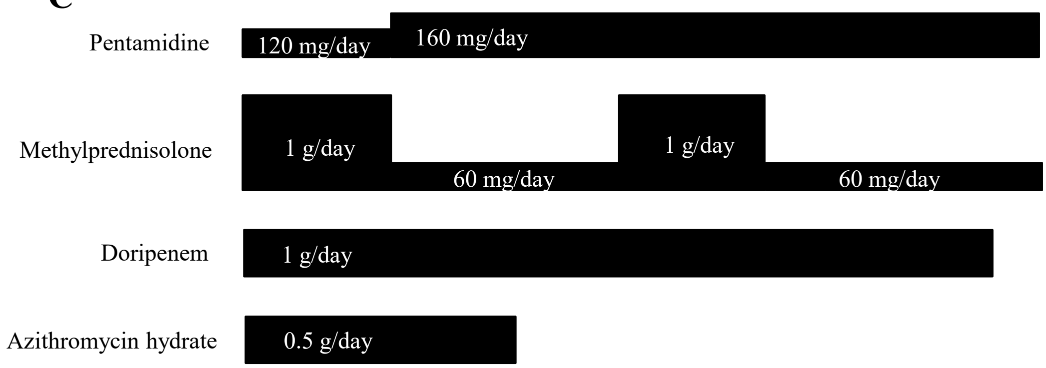


Fig. 1. Clinical course after admission.
A. Ventilator setting after admission.
A/C, assist/control (pressure control); SIMV, synchronized intermittent mandatory ventilation; CPAP, continuous positive airway pressure; PEEP, positive end-expiratory; PIP, peak inspiratory pressure.
B. PaO_2 /F_IO_2 ratio and dynamic compliance (Cdyn) of mechanical ventilation during the clinical course. During venovenous extracorporeal membrane oxygenation (V-V ECMO) administration, the PaO_2/F_IO_2 ratio and Cdyn of mechanical ventilation were accessed via the weaning test mode (mechanical ventilation setting; SIMV, F_IO_2 1.0, respiratory rate 20 breaths·min^{-1}, positive end-expiratory pressure 10 cmH_2O, peak inspiratory pressure 30 cmH_2O, V-V ECMO; seep gas flow 0 L/min, blood flow 1.0 L/min).
C. Therapeutic drugs used during mechanical ventilation.

to F_IO_2 0.4, RR 6 breaths·min^{-1}, PEEP 10 cmH_2O, and PIP 16 cmH_2O. On day 8, we again administered intravenous methylprednisolone at a dose of 1 g·day^{-1} for 3 days, followed by prednisolone at a dose of 60 mg·day^{-1}. The PaO_2/F_IO_2 ratio and Cdyn gradually increased in the V-V ECMO weaning test (mechanical ventilation setting for weaning test; SIMV, F_IO_2 1.0, RR 20 breaths·min^{-1}, PEEP 10 cmH_2O, PIP 30 cmH_2O: ECMO setting for weaning test; sweep gas flow 0 L·min^{-1}, blood flow 1.0 L·min^{-1}) (Fig. 1). PEEP was maintained at no less than 10 cmH_2O. On day 13, the PaO_2/F_IO_2 ratio and Cdyn increased to 462 (PaO_2 462 torr with F_IO_2 1.0) and 82.0 mL·cmH_2O^{-1}, respectively, under the weaning test. The ground-glass opacity and consolidation in the chest CT showed improvement (Fig. 2C). The patient was withdrawn from V-V ECMO on day 15. Pentamidine therapy was switched to atavaquone at a dose of 1.5 g·day^{-1}. She was discharged from the hospital on day 70. At 35 days after discharge from the hospital, the ground-glass opacity and consolidation had completely disappeared (Fig. 2D).

Discussion

The mortality of PJP patients receiving mechanical ventilation is 50-60%, regardless of HIV infection status (Mansharamani et al. 2000). Higher PEEP and development of pneumothorax are associated with increased mortality (Bedos et al. 1999; Festic et al. 2005; Boonsarngsuk et al. 2009). Pneumomediastinum is a factor related to poor prognosis in patients with non-HIV PJP requiring ICU admission (Weng et al. 2016). The use of V-V ECMO has two major merits – avoiding harmful damage induced by mechanical ventilation and assistance with oxygenation (Yadav et al. 2017). V-V ECMO might be useful to avoid mechanical ventilation-induced barotrauma and volutrauma, which lead to pneumothorax and pneumomediastinum. Furthermore, V-V ECMO provides optimal oxygenation

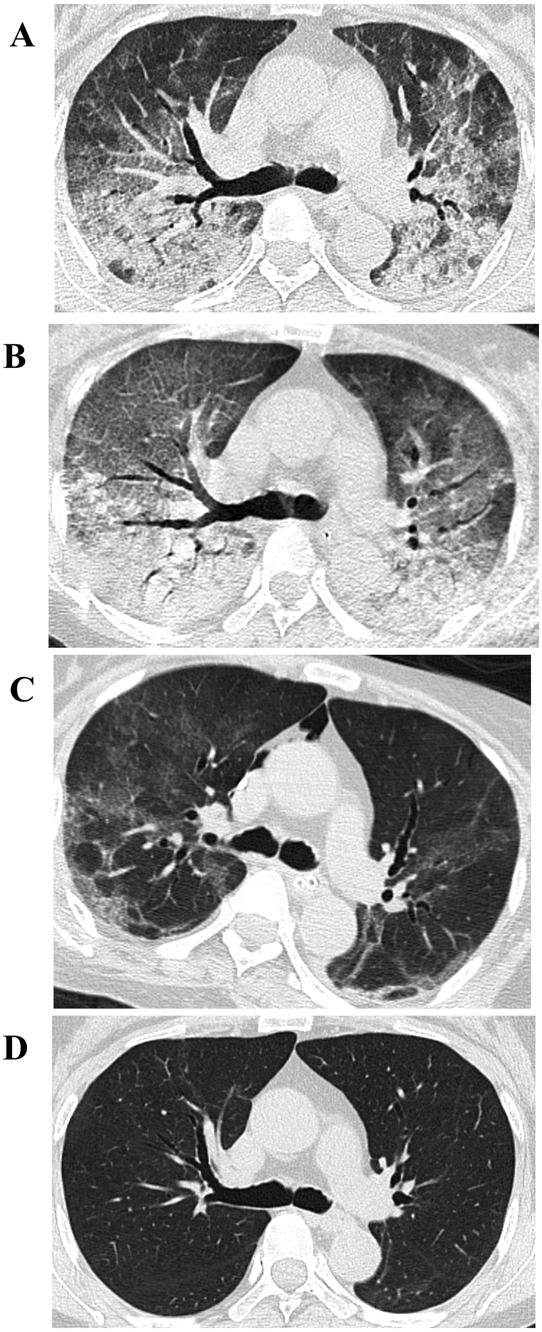


Fig. 2. Serial changes in chest high-resolution computed tomography (HRCT) findings.
A. A chest HRCT scan detected ground-glass opacity bilaterally in the lungs on admission.
B. Worsening of ground-glass opacity and consolidation was observed in the bilateral lung fields on day 5 after admission.
C. On day 13 (5 days after initiating V-V ECMO), the ground-glass opacity and consolidation had improved.
D. At 35 days after discharge from the hospital, the ground-glass opacity and consolidation had completely disappeared.

and avoids the toxic effects of hyperoxia that lead to constrictive atelectasis, increased vascular permeability, impaired tracheal mucus movement, and decreased surfactant production (Kallet and Matthay 2013). In our case, serial monitoring of PEEP, PaO_2/F_IO_2 ratio, and Cdyn were done in weaning test (Fig. 1A, B). We could reduce the PEEP to no less than 10 cmH_2O and increase the PaO_2/F_IO_2 ratio and Cdyn during V-V ECMO administration without inducing pneumothorax and pneumomediastinum. Not only PaO_2/F_IO_2 ratio, but also Cdyn, which reflects the airway resistance and elastic properties of the lung and chest wall, could be the good monitoring measurements during V-V ECMO from patients with non-HIV PJP.

The prognosis of non-HIV PJP patients who are managed by mechanical ventilation is usually poor. Choi et al. (2018) reported that the overall survival rate of non-HIV PJP who required mechanical ventilation was 32% (24 patients among 74 patients). The clinical characteristics of patients with PJP caused by other than HIV infection who were assisted with V-V ECMO are summarized in the Table 1 (n = 6). All the patients were younger than 60 years old. Five patients (83%) were under immunosuppressant therapy for pre-existing disease or transplantation. Five patients (83%) were treated with ECMO within 6 days after admission (the duration is unknown for one patient), and four patients (66.6%) survived. Although the summarized numbers of patients are limited, the survival rate might be better in patients with V-V ECMO assistance than those without V-V ECMO assistance in non-HIV PJP. As shown in Table 1, Geelhoed et al. (1974) reported three cases of non-HIV PJP who were managed with V-V ECMO 35 years ago. Two among three patients could not be rescued by V-V ECMO assistance, and one patient was introduced V-V ECMO in moribund state. V-V ECMO was temporarily effective for that patient; however, the patient could not keep on receiving ECMO assist because of the poor anticoagulation control. Recent mechanical and technical advances might improve the mortality even for such patients. Moreover, we have to think over the adaptive criterion of V-V ECMO in patients with non-HIV PJP, because V-V ECMO is costly and needs labour forces.

The adequate mechanical ventilator setting in patients with severe PJP is still unknown, especially during the V-V ECMO. We adopted A/C, followed by SIMV or continuous positive airway pressure (CPAP) for our case. In patients with acute respiratory distress syndrome (ARDS), the most frequent mechanical ventilation mode would be A/C, followed by SIMV (Checkley et al. 2008). There is no case-control study that proven the superiority of A/C to SIMV in clinical outcomes of ARDS. A/C mode could have the merit to reduce the random spontaneous breathing could be potentially harmful in increased work of breathing. On the other hand, a randomized control trial revealed that SIMV plus pressure support (PS) can safely and effectively improve oxygenation in patients with moderate ARDS (Luo et al. 2015). There is no previous study which compared the prognosis of patients with acute respiratory failure in the different ventilator setting mode during V-V ECMO. On one hand CESAR trail adopted PCV mode for ARDS,

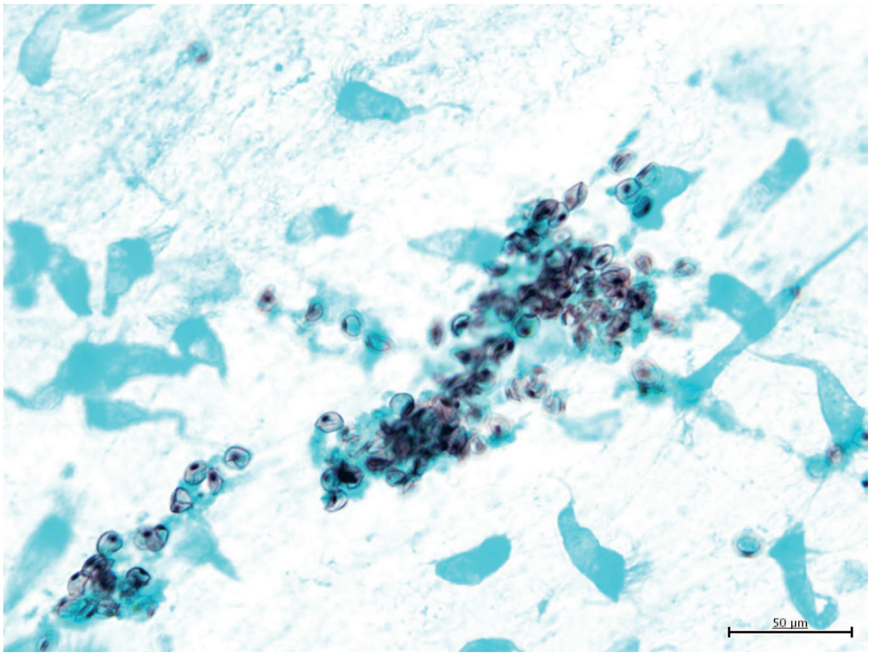


Fig. 3. Grocott staining of bronchoalveolar lavage (BAL) fluid.
Grocott staining-positive cysts (black color) were observed in the BAL fluid.

Table 1. Cases of *pneumocystis jirovecii* pneumonia with causes other than HIV infection managed with veno-venous extracorporeal membrane oxygenation.

Year	Author	Age	Sex	Underlying disease	Therapy for pre-existing disease	Initial PJP therapy	Duration from admission to ECMO	Duration of ECMO administration	Outcome
1974	Geelhoed et al.	12 Y	Male	leukemia	chemotherapy and corticosteroid therapy	pentamidine isethionate	4 days	5 days	Dead
		25 Y	Male	Hodgkin's Disease	radiotherapy and chemotherapy	pentamidine isethionate	Not stated	Not stated	Dead
		36 Y	Male	renal allograft	corticosteroid, azathioprine, antilymphocyte serum, focal x-irradiation	pentamidine isethionate	5 days	5 days	Alive
2012	Wu et al.	59 Y	Female	kidney transplantation	corticosteroid, tacrolimus, and mycophenolate mofetil	TMP/SMX	5 days	12 days	Alive
2018	Russell et al.	4 M	Male	Kaposiform hemangioma	corticosteroid, siroliums	TMP/SMX, methyl-predonisolone	4 days	7 days	Alive
2020	Nureki et al. (Present Case)	54 Y	Female	neuromyelitis optica	corticosteroid, azathioprine, methotrexate	pentamidine isethionate, methypredonosolone	6 days	6 days	Alive

M, month(s); Y, year(s); PJP, *pneumocystis jirovecii* pneumonia; TMP/SMX, trimethoprim/sulfamethoxazole; ECMO, extracorporeal membrane oxygenation.

but on the other hand REVA and EOLIA trials adopted A/C (volume control) (Peek et al. 2009; Schmidt et al. 2014). The Extracorporeal Life Support Organization (ELSO) guidelines recommend PCV for first 24 hours, PCV pulse spontaneous breaths after 24-48 hours, and PCV or CPAP plus spontaneous breaths after 48 hours for all ECMO patients.

ELSO recommends trial off by clamping sweep on vent rest settings PS ventilation or spontaneous breathing at 50% F_IO_2. Our ventilator setting during weaning test might be harmful because of high oxygen concentration (F_IO_2 1.0, RR 20 breaths·min^{-1}, PEEP 10 cmH_2O, PIP 30 cmH_2O). We recently revised the mechanical ventilation setting for weaning test as follows; $F_IO_2 < 1.0$ (if possible, < 0.6), RR 10-20 breaths·min^{-1}, PEEP 10-15 cmH_2O, and PIP < 30 cmH_2O (PS < 20 cmH_2O).

There are no randomized controlled drug study trials for PJP in non-HIV-infected patients. Drug therapy is usually administered according to the standard treatment applied to PJP patients with HIV; the first choice is TMP/

SMX therapy and the second choice is pentamidine therapy. We selected pentamidine therapy because the patient was treated with methotrexate, which may induce pancytopenia in combination with TMP/SMX therapy. We administered corticosteroid therapy to our patient, but the efficacy of adjuvant corticosteroid therapy in non-HIV-infected patients with PJP is controversial due to the lack of randomized controlled trials. The use of adjunctive corticosteroid therapy might accelerate recovery in cases of severe PJP in non-HIV-infected adults (Pareja et al. 1998). Early corticosteroid therapy for PJP in non-HIV-infected adults is not associated with better outcomes, including mortality, length of stay, admission to the ICU, or the need for mechanical ventilation (Wieruszewski et al. 2018). On admission, we administered high-dose corticosteroid therapy because we could not exclude the possibility of the other diagnosis, such as acute interstitial pneumonia, which might require high-dose corticosteroid. Moreover, it takes several days to obtain the results of PJP examination. We administered second high dose corticosteroid on day 8-10 because the decrease of PaO_2/F_IO_2 ratio.

Herein, we report a rare case of PJP in a non-HIV-infected patient who was successfully managed with VV-ECMO. V-V ECMO could be a useful tool for respiratory failure in patients with non-HIV PJP. Further accumulation of case data is necessary to clarify the significance of V-V ECMO in these patients.

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Conflict of Interest

The authors declare no conflict of interest.

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