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Extracorporeal membrane oxygenation as a successful salvage treatment in an HIV-positive patient with *Pnemocystis jirovecii* pneumonia

Izvantjelesna membranska oksigenacija kao uspješna spasonosna terapija u bolesnika s HIV infekcijom i upalom pluća uzrokovanom *Pnemocystis jirovecii*

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Case report

HIV-positive patients with *Pneumocystis jirovecii* pneumonia and severe respiratory failure have a high risk of mortality. In this paper we describe a case of a patient who was hospitalized for Pneumocystis pneumonia and newly diagnosed HIV-infection. His respiratory function deteriorated rapidly, necessitating early initiation of extracorporeal membrane oxygenation. The patient recovered well and was discharged after a prolonged hospital stay totaling 191 days. This paper highlights the use of veno-venous extracorporeal membrane oxygenation in patients with HIV-infection and pneumocystis pneumonia and provides a review of previously published literature on the same topic.

Prikaz bolesnika

Bolesnici s HIV-infekcijom i upalom pluća uzrokovanom *Pneumocystis jirovecii* te teškom respiratornom insuficijencijom imaju vrlo visoki rizik za smrtni ishod. U radu opisujemo slučaj bolesnika koji je hospitaliziran zbog pneumocystis pneumonije te novootkrivene HIV-infekcije. Njegova se respiratorna funkcija naglo pogoršavala, zahtijevajući rano uključivanje vantjelesne membranske oksigenacije. Bolesnik se dobro oporavio te je otpušten nakon produženog boravka u bolnici od ukupno 191 dan. Ovaj rad ističe korist primjene veno-venske izvantjelesne membranske oksigenacije u bolesnika s HIV-infekcijom i pneumocystis pneumonijom te nudi pregled literature na istu temu.

Introduction

Pneumocystis jirovecii pneumonia (PCP) incidence among HIV-infected patients is decreasing with the improvement of antiretroviral therapy, PCP prophylaxis and early diagnostics. However, the mortality still ranges from 10 to 60 %, with more fatal outcomes in patients requiring mechanical ventilation and those with CMV co-infection [1]. The mainstay of treatment is trimethoprim cotrimoxazole (TMP/SMX), but in severe cases concurrent corticosteroids are recommended, as well as mechanical ventilation in case of respiratory failure. Extracorporeal membrane oxygenation (ECMO) is indicated in hypoxic respiratory failure due to any cause that is potentially reversible, but HIV-infection has been usually regarded as a relative contraindication for this high-risk procedure. There have been few case reports of HIV-positive patients with PCP managed with ECMO in recent years (Table 1). We hope to add to this body of literature a report of a newly diagnosed patient with HIV and severe PCP with refractory respiratory failure, successfully managed with veno-venous ECMO (VV ECMO).

Case report

A 37-year old man presented to a county hospital with fever of 39 °C, dyspnea and malaise lasting a fortnight. He

Table 1. Information on patients with PCP and HIV treated with ECMO published until now

Tablica 1. Informacije o bolesnicima na ECMO-u s upalom pluća uzrokovanom *Pneumocystis jirovecii* i HIV infekcijom opisani u literaturi do sada

Ref	Author	Year of publication	Sex	Age	New or known HIV	HIV viral load	CD4+ count	Days to ART initiation	Days to ECMO	Duration of ECMO	CMV coinfection	IRIS	Pneumothorax	Vital status at discharge	Duration of hospitalization
[10]	Guterman	2005	M	55	New	80235	9	42	2	4	Yes	No	No	Alive	60
[11]	Goodman	2013	M	25	New	622234	36	N/A	18	69	No	Yes	No	Deceased	86
[11]	Goodman	2013	F	30	New	976631	13	17	3	73	No	No	Yes	Alive	35
[12]	Steppan	2013	M	39	N/A	6297	69	N/A	12	14	N/A	N/A	Yes	Deceased	26
[13]	Cawcutt	2014	M	45	New	11300	33	Before admission	13	57	No	Yes	Yes	Deceased	97
[14]	De Rosa	2014	F	21	Known	118330	2	N/A	8	20	No	No	Yes	Alive	N/A
[14]	De Rosa	2014	M	24	New	50728	3	8	10	24	No	No	No	Deceased	100
[15]	Ali	2016	M	26	New	907302	84	N/A	N/A	6	No	No	Yes	Alive	21
[16]	Guedes	2016	F	65	New	4050000	9	18	13	10	Yes	No	Yes	Alive	120
[17]	Horikita	2017	M	23	New	550000	9	3	3	26	No	Yes	No	Alive	62
[18]	Lee	2017	F	54	New	1075702	12	20	9	31	Yes	No	Yes	Alive	120
	Our patients	2018	M	37	New	85198	14	26	14	8	Yes	No	Yes	Alive	191

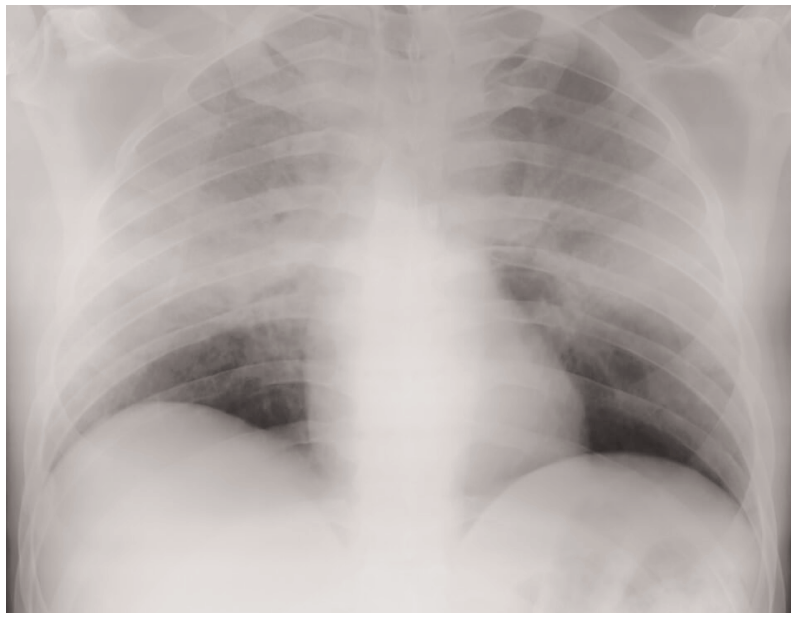

Figure 1. ARDS, bilateral consolidations sparing both lung bases (2nd day of hospital stay)

Slika 1. ARDS, bilateralne konsolidacije bez zahvaćanja obje plućne baze (2. dan hospitalizacije)

received a 7-day in-hospital treatment with levofloxacin for presumed community-acquired right sided pneumonia. At this time HIV serology was not performed. The patient remained febrile following discharge and his dyspnea worsened, becoming evident even on minimal exertion. He was readmitted to the same hospital two days later, and then transferred to the University Hospital for Infectious Diseases Zagreb after having tested positive to HIV-1. On clinical examination he was found to have oral cavity candidiasis and admitted to a 19 % body weight loss in the last two months. On admission he was tachypneic (40/min), tachycardic (140/min), with peripheral blood oxygen saturation of 96 % on oxygen flow of 10 L/min. His CD4+ T-cell count was 14 cells/μL, and HIV virus load of 85.198 copies/ml. Serologic testing revealed past infection with EBV, hepatitis A and immunity to hepatitis B due to natural infection. His CMV virus load was 318 copies/ml. His chest X-ray showed bilateral consolida-

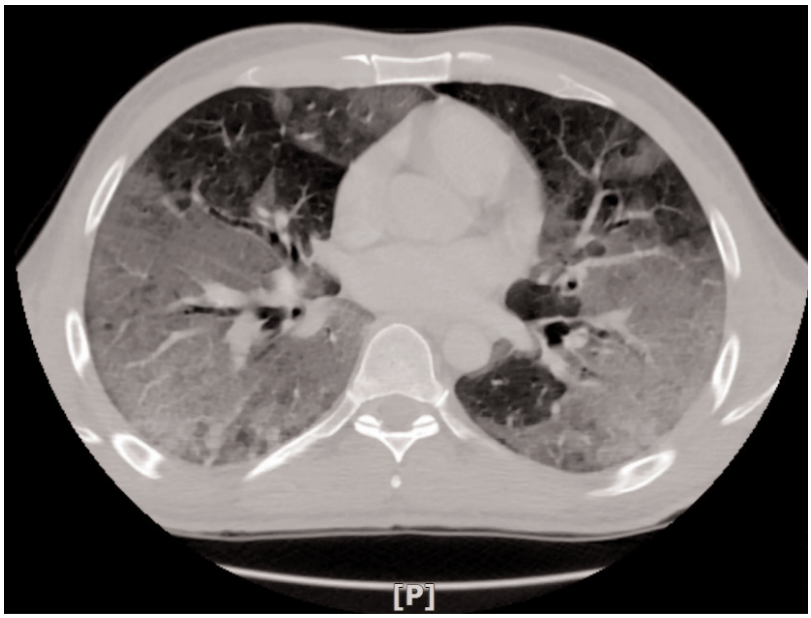

Figure 2. CT showing bilateral ground-glass infiltrates (2th day of hospital stay)

Slika 2. CT pokazuje bilateralne infiltrate uzorka "mliječnog stakla" (2. dan hospitalizacije)

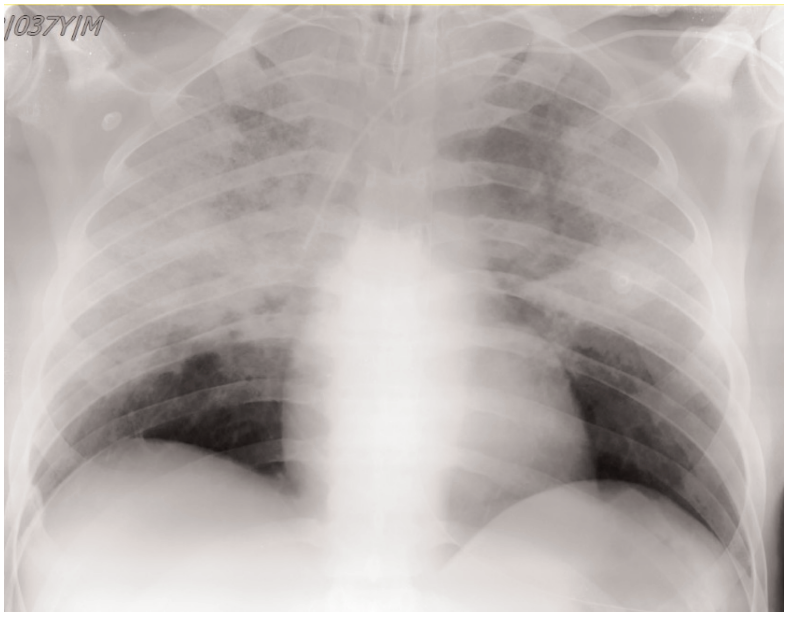

Figure 3. Worsening ARDS, patient on mechanical ventilation, with a central venous catheter inserted in the left subclavian vein (14th day of hospital stay)

Slika 3. Progresija ARDS-a, bolesnik na mehaničkoj ventilaciji s centralnim venskim kateterom postavljenim u lijevu potključnu venu (14. dan hospitalizacije)

tions indicative for acute respiratory distress syndrome (ARDS) (Figure 1). The patient's chest CT showed bilateral ground-glass infiltrates (Figure 2). He was immediately started on trimethoprim/sulfamethoxazole (TMP/SMX, 120 mg TMP q6h iv) and steroids (methylprednisolone 250 mg q24h iv) for presumed pneumocystis pneumonia (PCP). He remained febrile and his chest X-ray showed progression of lung infiltrates, and his CMV viral load increased to 787 copies/ml. Valacyclovir (500 mg q12h iv) was added to his therapy from 9th day of hospitalization. Bronchoalveolar lavage detected *P. jiroveci* by PCR, and CMV viral load of 24290 copies/mL. Despite treatment, he continued to deteriorate, and he was admitted to the intensive care unit (ICU) on the 14th day of hospital stay due

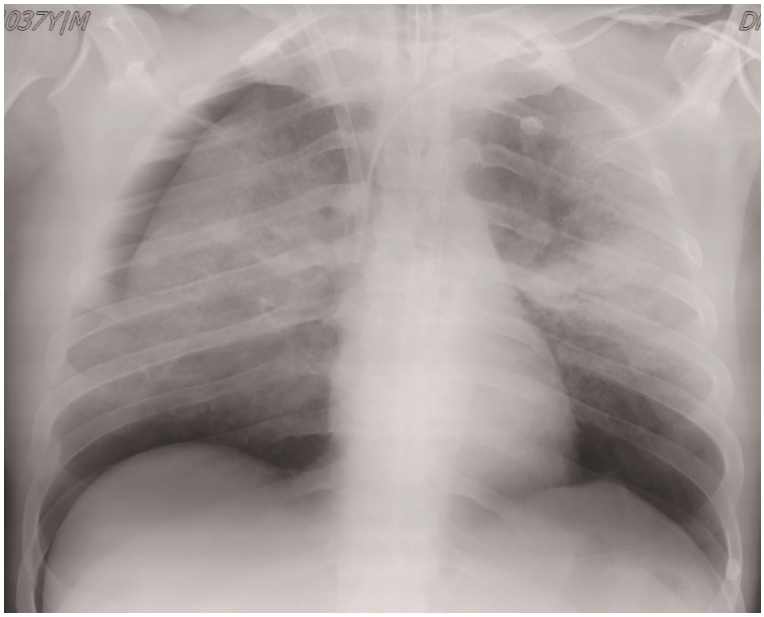

Figure 4. Patient on ECMO (44th day of hospital stay)
Slika 4. Bolesnik na ECMO-u (44. dan hospitalizacije)

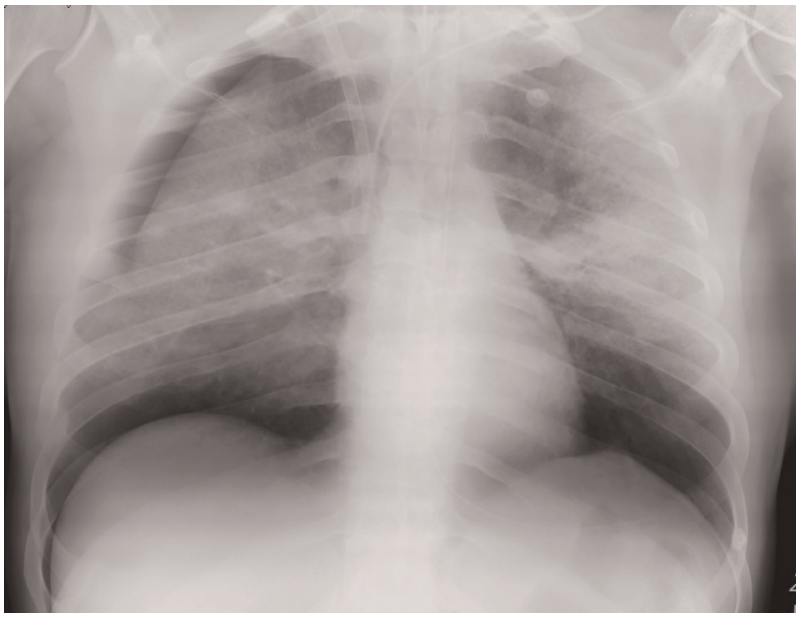

Figure 5. Multiple bilateral pneumothoraces with 4 simultaneous thoracic drains (45th day of hospital stay)
Slika 5. Multipli bilateralni pneumotoraksi (45. dan hospitalizacije)

to worsening of respiratory insufficiency (75 % oxygen saturation on 15 L/min oxygen flow, respiratory rate of 40/min, cardiac pulse 140/min). He was initially non-invasively ventilated, but after an hour intubated and mechanically ventilated (respiratory rate 20 breaths/min, tidal volume 8 mL/kg, FiO2 70 %, PEEP +6). However, he continued to deteriorate rapidly, both clinically and on imaging (Figure 3). While on minimally aggressive mechanical ventilation, his arterial blood gas analysis was severely abnormal (pH 6.934, pCO2 19.7 kPa, pO2 12.7 kPa, pO2 to FiO2 ratio 95 and alveolar arterial gradient of 0.29). At this time the patient's Murray score was 2.75, APPS score 4 and oxygenation index (OI) 42.6. He was therefore admitted to the ICU and initiated on VV ECMO using a 23F femoral and 19F jugular cannulas, with circuit flow 5 L/min, sweep gas of 6 L/min and oxygen (FiO2 of 1.0). Ventilator settings included respiratory rate of 18 breaths/min, tidal volume of 4 mL/kg, PEEP 5 cmH20 (Figure 4).

ECMO support was weaned after 8 days, while continuing valacyclovir for a total of 2 weeks, TMP/SMX for 5 weeks (continuing prophylactic dose afterwards) and was slowly weaned off steroids for 9 weeks. He was started on ART (abacavir/lamivudine and dolutegravir) on the 26th day of hospital stay, and one week later his CD4+ count was 21 cells/μl, and HIV viral load undetectable. His hospital stay was further complicated with multiple recurrent bilateral pneumothoraces (Figure 5), persisting over the course of 7 weeks, despite bilateral thoracic drainage. He acquired nosocomial sepsis and cholecystitis and was intermittently dependent on vasopressors during ICU stay as well. No dialysis was warranted. Due to prolonged mechanical ventilation, tracheotomy was performed. The patient was finally weaned off mechanical ventilation after 58 days, transferred out of ICU after 66 days, and tracheostomy decannulation was eventually performed. Three months since admission, the patient's CD4+ count was 86 cells/μL, and HIV viral load 116 copies/mL. He was finally discharged after 191 days of hospitalization, fully conscious, independently mobile, with no need for oxygen supplementation, continuing ART and PCP prophylaxis.

Discussion

We describe a patient with newly diagnosed late-presenting HIV-infection and severe PCP and CMV pneumonia with many complications including severe ARDS requiring use of VV ECMO and multiple bilateral pneumothoraces, who recovered following prolonged hospital stay of 5 months.

PCP course of illness can vary, with majority of patients recovering following treatment with TMP/SMX and adjuvant corticosteroids. In general, survival of HIV-infected patients admitted to the ICU is comparable to general population [2]. The incidence of pneumothorax complicating pneumonia is reported to be 4.5 %, with *Pneumocystis pneumonia* distinguished as the most frequent causative pathogen [3]. In patients with PCP, particularly newly diagnosed with HIV, ICU admission, mechanical ventilation and development of pneumothorax are factors associated with poor outcomes, with mortality up to 70 % [4].

Our patient was admitted to hospital with clinically and radiologically evident pneumonia and newly diagnosed HIV. Despite initiation of TMP/SMX and steroids, his respiratory insufficiency persisted. Due to CD4+ cell count <100 cells/μL, progression of pulmonary infiltrates despite therapy for PCP, and high CMV viral load on bronchoalveolar lavage, it was decided that valacyclovir should be added to therapy as CMV pneumonia can increase mortality in HIV-infected patients with PCP [1, 5]. Antiretroviral therapy was not introduced immediately for caution of developing immune reconstitution inflammatory syndrome (IRIS) which has been described in patients with PP [6]. Although commencing ART within 14 days from starting PCP treatment has been reported to improve outcome [7, 8], there are no clear guidelines for patients on mechanical ventilations and in ICU, where gastrointestinal absorption is impeded and there may be interactions with other medication.

Progressive respiratory insufficiency in our patient eventually required intubation and mechanical ventilation, but since the patient remained severely hypoxemic and rapidly developed respiratory acidosis, a decision was made that same day to initiate salvage management with VV ECMO. Extracorporeal life support organization (ELSO) Guidelines for adult respiratory failure indicate ECMO in acute heart or respiratory failure with high mortality risk despite optimal therapy, especially when PaO2/FiO2 is less than 100 on FiO2 > 90 %, Murray score is higher than 3, AOI score higher than 80, and APPS score higher than 8 [9]. Our patient did not fit all of the criteria, with a Murray score of 2.75, APPS 4 and AOI 42.6, but it was decided to start VV ECMO due to severe acidosis and lung protection from barotrauma. It is possible this early initiation on ECMO is the reason our patient recovered well.

ELSO guidelines list major immunosuppression as one of the contraindications, and although HIV-infection is not specifically mentioned, ECMO has not been routinely used in the treatment of HIV-infected patients with PCP. There are 9 publications reporting its use in 11 patients worldwide, recently increasing in number (Table 1). Of the 12 patients (including the one we reported), 10 were newly diagnosed with HIV-infection, median HIV viral load was 334165 (6297–4050000), median CD4+ cell count 13 (2–84), 11 were initially started on TMP/SMX. Time from hospital admission to ECMO was a median of 10 (2–18) days, 11 patients were on VV-ECMO, and the median duration of ECMO was 17 (4–69) days. Four (33.3 %) patients were treated for CMV pneumonia, 3 (25 %) were started on ART prior to ECMO, 3 (25 %) developed IRIS, 8 (66.7 %) developed pneumothorax. Out of 12 patients, 8 (66.7 %) survived to discharge, with a median hospital stay of 86 (21–191) days.

Conclusion

Our case report adds to the amounting evidence of positive role of VV ECMO as salvage management of HIV-positive patients with PCP who develop severe ARDS. ECMO allows less aggressive mechanical ventilation which is beneficial in patients with PCP who are prone to developing pneumothorax. Further knowledge can be gained from more similar cases and tracking long-term outcomes in these patients.

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