Extracorporeal Membrane Oxygenation in a Severely Immunosuppressed HIV Patient with Pneumocystis jirovecii Pneumonia: A Case Report and Review of Literature

Mariana Guedes*, Paulo Figueiredo, António Sarmento, and Lurdes Santos
Department of Infectious Diseases, Centro Hospitalar S. João, Portugal

Abstract

Pneumocystis jirovecii pneumonia is a very common opportunistic infection in HIV infected patients. Respiratory failure is a potential complication even with proper treatment. Nowadays, extracorporeal membrane oxygenation (ECMO) is a rescue therapy in patients with hypoxemia refractory to invasive ventilation. Although there are some concerns about its use in immunosuppressed patients, it could mean the last chance to some of them. We describe a case of Pneumocystis jirovecii pneumonia in a severely immunosuppressed patient successfully managed with ECMO.

ABBREVIATIONS

HIV: Human Immunodeficiency Virus; ECMO: Extracorporeal Membrane Oxygenation

INTRODUCTION

Pneumocystis jirovecii pneumonia (PCP) continues to be one of the most frequent opportunistic infections in HIV immunosuppressed patients, particularly on late diagnosed patients [1,2].

The use of extracorporeal membrane oxygenation (ECMO) in HIV infected patients is controversial. Although immunosuppression is a relative contraindication for ECMO support, this could be a salvage therapy for patients with severe respiratory failure not responsive to mechanical ventilation [3].

Although a few cases of Pneumocystis jirovecii pneumonia successfully treated under ECMO support have been reported in literature there are still some doubts regarding the clinical management of this situation [4-9].

CASE PRESENTATION

A 65 years old female with underlying history of hyperthyroidism, hypertension, dyslipidemia, mild mitral valve insufficiency and pulmonary bronchiectasis without known chronic respiratory insufficiency presented to the emergency department with complaints of fever, cough and dyspnea for two weeks. She also complained of loss of appetite and had a weight loss of 20 kg in the last 6 months. Prior to admission, she has been on treatment with oral amoxicillin plus clavulanic acid without clinical improvement.

On admission she had fever (temperature 38°C), tachycardia (heart rate 120 bpm), normal blood pressure, oral thrush, tachypnea (respiratory rate 26 bpm) and bilateral crackles on pulmonary auscultation.

Her blood analyses revealed anemia (hemoglobin 7.7g/dL) and lymphopenia (1.9 x 10^9/L), liver enzymes and renal function were normal and C-reactive protein was elevated (191.3 mg/L). Arterial blood gas analysis showed hypoxia: fraction of inspired oxygen (FiO2) 21% pH 7.49; partial pressure of carbon dioxide in arterial blood (PaCO2) 40 mmHg; partial pressure of oxygen in arterial blood (PaO2) 63 mmHg; ratio of partial pressure arterial oxygen and fraction of inspired oxygen (PaO2/FiO2 ratio) 300. Chest radiograph showed bilateral pulmonary infiltrates and chest high resolution computed tomography scan (HRCT-scan) showed diffuse bilateral ground glass opacities.
A community acquired pneumonia diagnosis was made and treatment with oxygen supplementation and intravenous levofloxacin was started.

Acute respiratory failure worsened and 10 days after admission she was transferred to our hospital to the Infectious Diseases Intensive Care Unit (ICU) needing invasive ventilation support. The blood gas analysis before intubation was \( \text{FiO}_2 45\% \); \( \text{PaCO}_2 \) 32 mmHg; \( \text{PaO}_2 \) 74 mmHg; \( \text{PaO}_2/\text{FiO}_2 \) ratio 164. Chest radiography on ICU admission after intubation presented with bilateral opacities (Figure 1). All bacteriological studies (sputum and blood cultures) performed in the first hospital were negative and HIV serology requested in the first hospital was positive.

On admission to our Infectious Diseases ICU a bronchoscopy was performed, previous antibiotics were stopped and empiric treatment for \textit{Pneumocystis jirovecii} pneumonia (PCP) with intravenous trimethoprim plus sulfamethoxazole (TMP/SMX) and prednisolone was started. The diagnosis was confirmed 4 days later with identification of \textit{Pneumocystis jirovecii} by immunofluorescence in broncho-alveolar lavage (BAL) samples. All investigation analyses for bacteria, virus, other fungi and mycobacteria (Ziehl-Neelsen, culture and DNA probes) performed in the BAL samples were negative.

Despite neuro-muscular paralysis, lung recruitment maneuvers and prone positioning, adequate gas exchange was not possible to achieve. On day 3 after ICU admission the patient was not responding to ventilatory support [pressure control ventilation (PCV) with peak inspiratory pressure (PIP) 26 cmH\(_2\)O, positive end expiratory pressure (PEEP) 6 cmH\(_2\)O, tidal volume (VT) 300mL, \( \text{FiO}_2 \) 50\%], with worsening of gas exchange: discrete worsening of hypoxia with a \( \text{PaO}_2/\text{FiO}_2 \) ratio 176, and of hypercapnia with \( \text{pH} 7.25 \) and \( \text{PaCO}_2 \) 64 mmHg. Murray score before cannulation was 2.75 (Table 1). No other organ failure was present.

ECMO support was started with a Cardiohelp\textsuperscript{\textregistered} with HLS\textsuperscript{\textregistered} oxygenator used in a veno-venous configuration with a femoral 25F cannula and a jugular 19F cannula. On ECMO, with 3.6 L/min of blood flow and gas sweep of 5 L/min, a protective ventilation was started (PCV with PEEP = 6 cmH\(_2\)O and PIP = 12 cmH\(_2\)O).

After 8 days on ECMO the patient had significant improvement of respiratory function, with resolution of radiological anomalies and adequate gas exchange under progressive reduction of gas sweep and blood flow. After a trial of discontinuing ECMO (normal arterial blood gases with zero gas sweep) the patient was disconnected from the by-pass on day 10 (Table 1).

Seven days after de-cannulation, there was a recrudescence of respiratory failure. The arterial blood gas analysis revealed worsening of hypoxemic respiratory failure and chest radiograph had new bilateral pulmonary infiltrates. The patient continued on invasive mechanical ventilation and in spite of adjustment of ventilatory parameters there was no clinical improvement. Prone positioning was started and bronchoscopy was repeated. Numerous forms of \textit{Pneumocystis jirovecii} were identified in the immunofluorescence of BAL samples and positivity for cytomegalovirus (CMV) DNA was also found. Quantification of CMV viral load was not performed. There were no lesions consistent with Kaposi Sarcoma on bronchoscopy and all other microbiologic exhaustive study performed in the BAL samples of the second bronchoscopy were negative.

Since our patient continued to have a high burden of \textit{Pneumocystis} forms in the BAL samples despite being on the twentieth day of intravenous TMP/SMX, treatment was prolonged in order to complete 21 days of intravenous TMP/SMX after de-cannulation. Treatment for cytomegalovirus (CMV) pneumonia with intravenous ganciclovir was also started because of molecular identification on BAL and blood CMV antigen positivity (71 cells). CMV retinitis was excluded by ophthalmological observation. Imipenem and linezolid were also added considering a possible ventilator-associated pneumonia.

Confirmation of HIV-1 infection was performed with Western Blot analysis. Complimentary workup for HIV infection revealed a viral load of 4,050,000 copies/mL (6.61 log\textsuperscript{10}) and CD, lymphocyte count of 9 cells/mm\textsuperscript{3}. Resistance test for reverse-transcriptase (nucleoside and non-nucleoside) and protease inhibitors and genetic analyses for HLA B5701 were negative.
Highly active anti-retroviral therapy (HAART) with tenofovir/emtricitabine plus dolutegravir was started 5 days after decannulation (day 17 after ICU admission). Oral TMP/SMX in prophylactic doses (960mg 3 times per week) was started after completing the induction TMP/SMX treatment.

There was progressive clinical improvement of respiratory failure allowing weaning of ventilatory support with tracheotomy and respiratory rehabilitation. Forty days after disconnection from ECMO support the patient was transferred to the Infectious Diseases ward. On day 67 of hospital admission, she developed a spontaneous left pneumothorax (Figure 2A) that was successfully drained with a chest tube (Figure 2B).

After almost 4 months of hospital admission she was discharged with some dyspnea when walking for little distances (10 meter) and during her activities of daily living. Oxygen supplementation (blood gas analysis on discharge with FiO2 21%; pH 7.48; PaCO2 42.2 mmHg; PaO2 60.8 mmHg; PaO2/FiO2 ratio 289) and physical rehabilitation were prescribed. She continued on tenofovir/emtricitabine plus dolutegravir and TMP/SMX prophylaxis. Six months after starting HAART, viral load was suppressed (below 20 copies) and CD4 cell count increased to 43 cells/mm3.

**DISCUSSION**

The most important risk factor for *Pneumocystis jirovecii* pneumonia is immunosuppression, particularly HIV infection. With widespread use of HAART and PCP prophylaxis, the incidence of this disease has decreased, being more common in patients who are unaware of HIV infection or noncompliant with medications. Late diagnosis with evolution to respiratory failure, still occur, being HIV and PCP diagnosed simultaneous with ICU admission.

This is a subtle disease that can mimic a wide variety of infectious and noninfectious conditions. Patients usually complain of progressive dyspnea, fever and a nonproductive cough, with symptoms lasting for weeks before seeking medical care.

On hospital admission they can have respiratory insufficiency, and unlike non-HIV immunosuppressed patients, they frequently evolve with clinical worsening after starting treatment. Some of those patients will develop respiratory failure, needing intensive care admission for ventilatory support [1,2].

ECMO support is a rescue therapy in patients who do not respond to conventional invasive ventilation. Its use is indicated in patients with hypoxic respiratory failure and/or CO2 retention refractory to conventional mechanical ventilation [3]. This technique is useful in acute respiratory distress syndrome (ARDS) allowing rest lung settings with permissive hypercapnia [3,10].

This report describes a case of *Pneumocystis jirovecii* pneumonia in a late diagnosed HIV patient. The delay in diagnosing of HIV infection and starting the appropriated treatment for PCP may have played a role in progressive worsening of respiratory failure.

Facing a deteriorating CO2 washout from the patient native pulmonary function, that we could not cope with invasive ventilation, we considered respiratory ECMO, despite malnutrition and bad condition of this patient. Since patients

**Table 2: Case reports of HIV infected patients with *Pneumocystis jirovecii* Pneumonia requiring ECMO.**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age (years) / Gender</th>
<th>Pre-ECMO invasive ventilation (days)</th>
<th>Pre-ECMO P/P ratio; PaCO2; PaO2; P/F ratio</th>
<th>Duration of ECMO (days)</th>
<th>CD4 count (cells/mm3)</th>
<th>Viral load (copies/mL)</th>
<th>Anti-PCP treatment</th>
<th>Timing of HAART initiation</th>
<th>Pneumothorax</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Our patient</td>
<td>65/F</td>
<td>3</td>
<td>253;5.5;4.7;2.5</td>
<td>10</td>
<td>9</td>
<td>4.050.000</td>
<td>TMP/SMX</td>
<td>Post-ECMO</td>
<td>Yes</td>
<td>Survived</td>
</tr>
<tr>
<td>Gutermann et al (4)</td>
<td>65/M</td>
<td>4</td>
<td>NR;NR;NR</td>
<td>4</td>
<td>9</td>
<td>80.235</td>
<td>TMP/SMX</td>
<td>No</td>
<td>Survived</td>
<td></td>
</tr>
<tr>
<td>Steppan (7)</td>
<td>39/M</td>
<td>8</td>
<td>NR;NR;NR</td>
<td>14</td>
<td>69</td>
<td>6297</td>
<td>CLP+PL then ATQ, then TMP/SMX</td>
<td>Pre-ECMO</td>
<td>Yes</td>
<td>Died</td>
</tr>
<tr>
<td>Goodman et al (6)</td>
<td>25/M</td>
<td>NR</td>
<td>63.6;5.29;7.38</td>
<td>69</td>
<td>36</td>
<td>622.34</td>
<td>PL, then CLP+PQ, then TMP/SMX</td>
<td>Pre-ECMO</td>
<td>No</td>
<td>Died</td>
</tr>
<tr>
<td>Goodman et al (6)</td>
<td>30/F</td>
<td>3</td>
<td>50.1;4.6;7.39</td>
<td>7</td>
<td>13</td>
<td>976.631</td>
<td>TMP/SMX</td>
<td>Post-ECMO</td>
<td>Yes</td>
<td>Survived</td>
</tr>
<tr>
<td>De Rosa et al (7)</td>
<td>21/F</td>
<td>NR</td>
<td>120;NR;NR</td>
<td>20</td>
<td>2</td>
<td>118.330</td>
<td>TMP/SMX, then CLP+PQ</td>
<td>No</td>
<td>Survived</td>
<td></td>
</tr>
<tr>
<td>De Rosa et al (7)</td>
<td>24/M</td>
<td>NR</td>
<td>100;NR;NR</td>
<td>24</td>
<td>3</td>
<td>50.728</td>
<td>TMP/SMX, then CLP+PQ+ATQ</td>
<td>During ECMO</td>
<td>No</td>
<td>Died</td>
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<tr>
<td>Cawcutt et al (9)</td>
<td>45/M</td>
<td>NR</td>
<td>50;NR;NR</td>
<td>57</td>
<td>33</td>
<td>113.000</td>
<td>TMP/SMX, CLP+PQ</td>
<td>Pre-ECMO</td>
<td>Yes</td>
<td>Died</td>
</tr>
<tr>
<td>Ali et al (8)</td>
<td>26/M</td>
<td>1</td>
<td>200;10;9;7.01</td>
<td>6</td>
<td>64</td>
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<td>TMP/SMX</td>
<td>Post-ECMO</td>
<td>Yes</td>
<td>Survived</td>
</tr>
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</table>

**Abbreviations:** ECMO: Extracorporeal Membrane Oxygenation; PCP: *Pneumocystis jirovecii* Pneumonia; HAART: Highly Active Anti-Retroviral Therapy; P/P ratio: Ratio of Partial Pressure Arterial Oxygen and Fraction of Inspired Oxygen (mmHg); PaCO2: Partial Pressure Of Carbon Dioxide In Arterial Blood (mmHg); TMP: Trimethoprim; SMX: Sulfamethoxazole; CLI: Clindamycin; PI: Pentamidine; ATQ: Atovaquone; PQ: Primaquine; NR: Not Reported
analyses were negative except numerous forms of Kaposi Sarcoma on bronchoscopy and all microbiological of respiratory failure. There were no lesions consistent with pneumatoceles are common sequelae.

were reported (Table 2). All the reported ones are in severely could guide dosing recommendations are still missing. TMP/SMX and knowledge about drug membranes removal that patient improved allowing weaning. Pharmacokinetics studies of dosing could have been subtherapeutic during ECMO; slowly the membranes removal of TMP/SMX, we consider that antimicrobial patient had started HAART 2 days before clinical worsening. reconstitution inflammatory syndrome (IRIS jirovecci

was unlikely since the patient had started HAART 2 days before clinical worsening. The patient was on intravenous TMP/SMX so there were no compliance issues. By that time the patient was on the seventieth day after de-cannulation, on the twentieth day of TMP/SMX treatment and under corticoids weaning. Considering the clinical and radiological respiratory worsening at this time and the lack of pharmacokinetics studies about polymethylpentene ECMO membranes removal of TMP/SMX, we consider that antimicrobial dosing could have been subtherapeutic during ECMO; slowly the patient improved allowing weaning. Pharmacokinetics studies of TMP/SMX and knowledge about drug membranes removal that could guide dosing recommendations are still missing.

Few cases of ECMO support in HIV patients with PCP were reported (Table 2). All the reported ones are in severelyimmunosuppressed patients with a CD4 count less than 100 cells/mm [3]. They are young adults with age between 21 and 55 years old, our patient being the older one with 65 years. Similar to our report, other authors have expressed their doubts about TMP/SMX therapy efficacy during ECMO [4-9]. In the published literature, adding another antibiotic does not seem to improve outcome [7,8]. However, due to the few clinical reports and poor prognosis of these patients, we cannot take conclusions regarding this therapy.

With worldwide implementation of ECMO technique, more HIV patients will be considered for ECMO support. HIV infected patients with PCP and respiratory failure usually have a poor prognosis with a high mortality and an increased risk for nosocomial infections. In literature, the mortality rate of these patients under ECMO is around 50% [4-9]. These data can help clinics in considering if and when to start ECMO support, although in advanced immunosuppression is always a difficult decision.

REFERENCES


