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Varicella associated acute respiratory distress syndrome in an adult patient: an example for extracorporeal respiratory support in Brazilian endemic diseases

Síndrome da angústia respiratória aguda associada à varicela em paciente adulto: exemplo de suporte respiratório extracorpóreo em doenças endêmicas brasileiras

ABSTRACT

A case of a 30 year-old man presenting with severe systemic chickenpox with refractory hypoxemia, central nervous system vasculitis and anuric renal failure is described. Ambulance transportation and support using veno-venous extracorporeal membrane oxygenation were necessary

until the patient recovered. Ultimately, the potential use of extracorporeal membrane oxygenation support in low-middle income countries to manage common diseases is discussed.

Keywords: Extracorporeal membrane oxygenation; Respiratory failure; Respiration, artificial; Chickenpox; Intensive care units; Case reports

INTRODUCTION

Worldwide, several infectious diseases have a high mortality rate. Three of the top ten causes of death listed by the World Health Organization are infectious diseases.⁽¹⁾ Additionally, new infectious agents are occasionally detected, some of which result in a high number of fatalities, such as influenza A (H1N1) in 2009.

Primary varicella, or chickenpox, is usually a benign childhood illness. Despite the fact that fewer than 10% of cases occur in adults, the risk of death for adults with chickenpox is 23 to 29 times higher than in children.⁽²⁾ Furthermore, pneumonitis is the most serious complication and the most common cause of death among adults with this illness.⁽³⁾ We report a case of chickenpox in a non-immunocompromised adult with severe pneumonitis, central nervous vasculitis and acute renal failure who needed veno-venous extracorporeal membrane oxygenation (ECMO) support.

CASE PRESENTATION

A previously healthy 30 year-old man was admitted to the emergency room with a five day history of cutaneous vesicles, fever and dyspnea. His daughter was in the convalescence phase of chickenpox. He was cyanotic and in moderate respiratory distress. The chest x-ray and appearance of the skin at the time the patient presented are shown in figures 1A and 1B, respectively.

The clinical diagnosis was chickenpox with pulmonary manifestation. At this time, renal and hemodynamic functions were normal. Therapy with acyclovir

was initiated, and the patient was admitted to the intensive care unit (ICU) for monitoring and respiratory support. On the first day of ICU stay, he developed unrelenting respiratory distress; he was intubated, and mechanical ventilation was initiated. His hemodynamic and renal status deteriorated. During the first week of ICU stay, he required up to 0.3mcg/kg/minute of norepinephrine, and the cumulative fluid balance was positive at approximately 40 liters despite peritoneal dialysis. In addition to the renal and hemodynamic dysfunctions, his pulmonary function also deteriorated, and he developed severe hypoxemia on the eighth day after admission (Table 1). This condition was unresponsive to an alveolar recruitment maneuver and a positive end-expiratory pressure (PEEP) of 22cmH₂O (Table 1). At this time, it was thought that the patient had ventilator associated pneumonia, and he was treated with vancomycin and imipenem. Next, ECMO support was indicated, and the ECMO group *Hospital das Clínicas de São Paulo* was contacted. The patient was cannulated in situ using a percutaneous technique with 19 and 21 French cannulae through the left jugular (atrial cannula) and femoral (drainage cannula) veins, respectively. The venous-venous ECMO support was initiated with 5L/minute of blood and gas flow. The mechanical ventilation was adjusted with PEEP=10cmH₂O, driving pressure=10cmH₂O, respiratory rate=10 breaths/minute, and the ventilator FiO₂ was progressively lowered to 0.6. The norepinephrine infusion was promptly stopped due to hemodynamic improvement. The patient developed diffuse cutaneous and conjunctive petechiae, highly suggestive of vasculitis; therefore, anticoagulation with heparin was not initiated due to the possibility of central nervous system bleeding, once tomography was not locally available and the Richmond agitation sedation scale (RASS) was minus five.

After four hours of clinical stabilization, the ECMO support was adjusted to 6L/minute of blood flow and 8L/minute of gas flow, and the mechanical ventilation settings were kept the same. Transportation by ambulance to downtown São Paulo City was required, which is a 156km journey lasting approximately two hours. For the transport, the ventilator FiO₂ was increased to 1.0.

After transportation, the ventilator FiO₂ was reduced again to 0.6, and the other ECMO and ventilator variables were similar to those used in the stabilization period. Continuous venous - venous hemofiltration was initiated with a progressively higher ultrafiltration rate, up to 350mL/hour. During the first day, the peripheral oxygen

saturation (SpO₂) dropped to 65%, despite ventilator FiO₂ and ECMO blood flow elevations to 1.0 and 6500mL/minute, respectively. At this point, a diagnosis of ECMO refractory hypoxemia was made. ECMO refractory hypoxemia has been defined as a PaO₂<50mmHg (taking precedence) or an arterial saturation persistently lower than 85%.⁽⁴⁾ In our patient, as the ECMO running time was <24 hours, the difference of color between the drainage and atrium cannulae was significant (despite high ECMO blood flow), and the pulmonary injury was severe (white lung on the x-ray - Figure 1A and respiratory static compliance=1.2mL/cmH₂O - Table 1), the diagnosis of ECMO blood re-circulation and artificial lung dysfunction was dismissed. ECMO refractory hypoxemia was attributed to the association between severely decreased native lung function and a low ECMO blood flow/cardiac output ratio.⁽⁴⁾

Therefore, a stepwise alveolar recruitment maneuver was performed using PEEPs from 25 to 45cmH₂O, with a driving pressure=15cmH₂O, an inspiratory time=3 seconds and a respiratory rate=10 breaths/minutes. After the initial PEEP=25cmH₂O, each step lasted 2 minutes, and the PEEPs used were 30, 25, 35, 25, 40, 25, 45, 25cmH₂O sequentially, as previously described.⁽⁵⁾ Finally, the ideal PEEP was titrated using the pressure point 2cmH₂O above the best dynamic respiratory compliance (C_{dyn}), measuring the C_{dyn} after the alveolar recruitment maneuver and decreasing the PEEP from 25cmH₂O each 2 minutes in 2cmH₂O steps, as previously described.⁽⁶⁾ The ideal PEEP measured was 25cmH₂O, which was used with a driving pressure of 5cmH₂O, inspiratory time=1 second, and a respiratory rate=10 breaths/minute. The SpO₂ 30 minutes after the alveolar recruitment maneuver and PEEP titration increased to 84%.

During the next twelve hours, the SpO₂ progressively increased to 92%. After this period, the ventilator FiO₂ and PEEP were gradually reduced, keeping the SpO₂≥85%. After four days, the patient was comfortable and ventilating with a PEEP=15cmH₂O, pressure support=6cmH₂O and FiO₂=0.3. The ECMO autonomy test was performed, setting the gas flow=0L/minute for 1 hour, as previously described.⁽⁷⁾ The chest x-ray at this point is shown in figure 1C. After ECMO decannulation, a central nervous system tomography was performed and showed multiple bleeding areas, which were highly suggestive of vasculitis (Figure 1D).

Sedation was withdrawn, and after 24 hours the patient was unresponsive with scanning movement of

Table 1 - Respiratory, hemodynamic and metabolic characteristics of the patient

	Pre-ECMO	After-ECMO	Day 1	Day 2	Day 3	Day 4	Day 5
Blood gases							
pH	7.51	7.40	7.38	7.37	7.47	7.49	7.42
PaO ₂ (mmHg)	39	54	31	89	58	54	60
PaCO ₂ (mmHg)	39	51	40	44	44	32	35
SBE (mEq/L)	+8.6	+6.1	+2.0	+0.1	+7.7	+1.1	-1.3
Mechanical ventilation							
Ventilatory mode	PCV	PCV	PCV	PCV	PCV	PCV	PSV
Tidal volume (mL)	500	12	15	110	150	160	200
FIO ₂	1.0	0.6	1.0	1.0	0.6	0.4	0.4
PEEP (cmH ₂ O)	22	10	10	25	23	19	15
Plateau pressure (cmH ₂ O)	45	20	20	30	28	24	20
Respiratory rate (breaths/minute)	30	10	10	10	10	10	10
Static compliance (mL/cmH ₂ O)	22	1.2	1.5	20	30	32	40
Hemodynamic support							
Norepinephrine dosage (mcg/kg/minute)	0	0	0.1	0.1	0.05	0	0
Renal support							
Cumulative fluid balance (mL)	-----	0	-754	-5124	-9824	-14960	-21266
Creatinine (mg/dL)	13.64	-----	11.71	10.98	6.37	2.77	2.73
BUN (mg/dL)	187	-----	135	123	62	65	61
CVVH (dosage - mL/kg)	No	No	37.5	37.5	50.0	50.0	37.5
ECMO support							
Blood flow (mL/minute)	-----	6500	6500	4800	4000	4000	4000
Gas flow (L/minute)	-----	11	12	10.5	8	4	1.5

The column Pre-ECMO indicates the eighth day after ICU admission. ECMO - extracorporeal membrane oxygenation; PaO₂ - partial pressure of oxygen; PaCO₂ - partial pressure of carbon dioxide; SBE - standard base excess; BUN - blood urea nitrogen; PCV - pressure controlled ventilation; PSV - pressure support ventilation; FIO₂ - fraction of inspired oxygen; PEEP - positive end-expiratory pressure; CVVH - continuous venous-venous hemofiltration. The post-dilutional CVVH run was performed using adenosine citrate dextrose 2.2% to enhance the hemofilter protection.

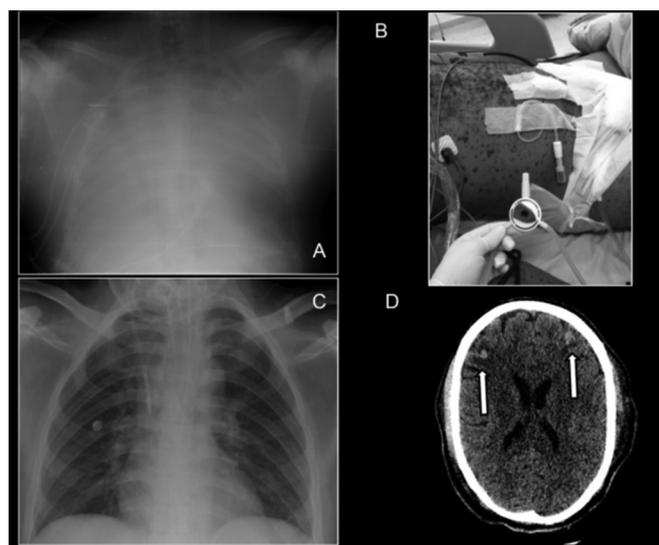


Figure 1 - Thoracic and central nervous system images. (A) The chest X-Ray after ECMO cannulation; (B) The cutaneous appearance of the patient. (C) The chest X-Ray on the day of ICU discharge; (D) The central nervous system tomography, the arrows indicate two of the multiple focal bleedings.

eyes. A tracheostomy was performed, and the mechanical ventilation was withdrawn. After eleven days, the patient was discharged from the ICU, the neurologic and renal function gradually recovered, and after thirty three days he was discharged from the hospital to his home.

DISCUSSION

ECMO respiratory support has been used worldwide to sustain the lives of patients with severe respiratory failure. The mortality associated with infectious diseases has been reduced in Brazil during the last decade. However, these infectious diseases are still the main cause of severe respiratory failure in middle income countries.⁽⁸⁾ Therefore, we would like to discuss the use of ECMO to support patients with some endemic infectious diseases in low-middle income countries, such as Brazil.

In England, from 1995 to 1997, seventy five adult patients died due to severe chickenpox (9.07/1,000,000 deaths), representing a mean of 25 deaths per year. From

those 75 patients, sixty died primarily due to chickenpox with severe respiratory failure. The majority of deaths were in young adult men (81%).⁽⁹⁾ Among adult and pediatric patients, viral pneumonia was the cause of severe respiratory failure in 27% of patients who required ECMO. Furthermore, up to 18% of these ECMO supported patients were young (mean age of 33 years old) and were diagnosed with severe chickenpox.⁽¹⁰⁾ Overall survival was 57-71%,^(10,11) the median time on ECMO support was seven days, and renal replacement therapy was necessary in 71% of patients.⁽¹¹⁾ ECMO support has been considered an important adjunct therapy in severe chickenpox in high-income countries.⁽¹²⁾ The severe renal and respiratory dysfunction both contributed to the hypoxemia of our patient. Moreover, the ECMO support allowed for the safe transportation of the patient in addition to sufficient time for the renal replacement therapy to be effective. The clinical approach for severe hypoxemia during ECMO support is discussed elsewhere.⁽⁴⁾

The influenza A H1N1 epidemics in 2009 had a hugely negative impact in Brazilian tertiary hospitals,⁽¹³⁾ resulting in unprecedented organizational responses.⁽¹⁴⁾ However, despite the local and government emergency measures, the case-fatality was higher than in other countries, mainly due to severe respiratory failure.⁽¹³⁾ In high income countries, the H1N1 pandemics led to extreme advanced resource mobilization in order to offer ECMO support to a high number of patients concomitantly. In Australia, elective surgeries, especially cardiac surgery, were suspended to open ICU beds and to re-allocate perfusion devices for ECMO support in the ICU.^(15,16) This policy resulted in a high number of ECMO supported patients and a high survival rate (78%).⁽¹⁷⁾ In England, three novel ECMO centers were built during the epidemics, and there was a high survival rate (76%).⁽¹⁸⁾ Other countries also needed to improve their ECMO support facilities during the H1N1 crisis, resulting in encouraging outcomes.^(19,20)

Malaria is another low-middle income country disease that potentially results in severe respiratory failure needing ECMO support. *Plasmodium vivax* and *Plasmodium falciparum* are the etiologies of respiratory failure in patients who required ECMO support. It is interesting to note that the ECMO support that is described in the literature was in patients who emigrated from low-middle income regions to high-income regions, likely reflecting

the cultural - economical incapacity of low-middle income countries to control the disease or to offer adequate support for the victims of severe malaria.^(21,22)

The Hantaan virus cardio-respiratory syndrome presentation with severe hypoxemia and refractory cardiovascular failure is associated with 100% mortality.⁽²³⁾ Although veno-arterial ECMO support has been described to support (cardiovascular and respiratory support) those patients with high death probability, with a survival rate of 61%.^(24,25)

Leptospirosis is a frequent tropical fever disease that can present with severe hypoxemia and alveolar hemorrhage.⁽²⁶⁾ The severe cardiovascular and respiratory failure can be refractory to optimized ICU therapy;⁽²⁶⁾ therefore, in this scenario, respiratory and cardiovascular ECMO support has been successfully used.⁽²⁷⁾ We would like to emphasize that the hemorrhagic lung disease did not prevent the success of ECMO support.⁽²⁸⁾

Tuberculosis is a prevalent disease in low-middle income countries and is a major health concern. However, severe respiratory and cardiovascular failure are not common. Those more severely ill patients have been supported with veno-arterial and/or veno-venous ECMO.^(29,30) Those descriptions of ECMO supported patients with tuberculosis were also in high income countries.

The incidence of dengue has increased 30 fold worldwide over the last 50 years. In 2014, several Brazilian states noted a significant rise in cases, with more than two hundred deaths.⁽³¹⁾ Although pulmonary hemorrhage is not frequent in severe dengue, the presence of pulmonary edema, pleural effusion and ARDS are associated with a high mortality.^(32,33) ECMO can be a feasible alternative support for this condition.

CONCLUSION

There are many prevalent diseases in low-middle income countries (such as Brazil) that affect the young, economically active population and that potentially cause severe respiratory and cardiovascular failure. The main policy of public health authorities must be focused on disease control. Secondly, some tertiary centers must be able to provide advanced respiratory and cardiovascular ECMO support for safe transportation and adequate care for those more severely ill patients.

RESUMO

Descreveu-se aqui o caso de um homem de 30 anos de idade com quadro de varicela grave, hipoxemia refratária, vasculite do sistema nervoso central e insuficiência renal anúrica. Foi necessário transporte por ambulância com suporte respiratório extracorpóreo veno-venoso, sendo este utilizado até a recuperação

do paciente. Discute-se o potencial uso de oxigenação por membrana extracorpórea em países em desenvolvimento para o controle de doenças comuns nestas áreas.

Descritores: Oxigenação por membrana extracorpórea; Insuficiência respiratória; Respiração artificial; Varicela; Unidades de terapia intensiva; Relatos de casos

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