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Case Report

Case report: The use of Venovenous Extracorporeal Membrane Oxygenation in the Treatment of Acute Respiratory Distress Syndrome in Severe Leptospirosis

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Abstract: Leptospirosis is a globally distributed zoonosis with a clinical spectrum ranging from mild febrile illness to life-threatening disease, that can result in acute kidney injury (AKI) and severe pulmonary complications such as alveolar hemorrhage and acute respiratory distress syndrome (ARDS). We present the case of a 20-year-old man with fever and respiratory distress, diagnosed with ARDS and AKI. Venovenous (VV), extracorporeal membrane oxygenation (ECMO) and sustained low-efficiency daily dialysis (SLED) were initiated. The patient showed significant respiratory improvement after eight days and renal recovery after seventeen days. Leptospirosis serological conversion confirmed the diagnosis. This case highlights the potential of VV ECMO as an effective supportive therapy in severe respiratory failure secondary to leptospirosis. Early recognition and aggressive management, including ECMO and daily dialysis, may enhance outcomes in severe pulmonary leptospirosis.

Keywords: Leptospirosis; Acute Respiratory Distress Syndrome; Extracorporeal Membrane Oxygenation.

1. Introduction

Leptospirosis is a zoonosis caused by spirochetes of the genus Leptospira [1, 2]. Risk factors include domestic exposure to infected rodents or pets, occupational exposure, recreational activities in freshwater environments and environmental conditions like flooding [3]. The incubation period ranges from two to 26 days, with a mean of approximately ten days [4]. Clinically, up to three-quarters of patients present with a mild, self-limiting febrile disease. However, about 10-20% of cases can progress to severe disease, driven by

an immune response that can involve various complications, including hyperbilirubinemia, acute kidney injury (AKI) and acute respiratory distress syndrome (ARDS) [1, 2]. In Brazil, an average of 3,846 cases and 375 deaths are confirmed each year. However, due to concerns about underdiagnosis, the actual disease prevalence may be significantly underestimated [5].

Patients with severe leptospirosis can present with diffuse alveolar hemorrhage. Severe pulmonary leptospirosis, especially when accompanied by refractory hypoxemia and resistance to mechanical ventilation, is associated with high mortality rates. Intensive care support is essential for managing severe respiratory failure in leptospirosis [6]. Extracorporeal membrane oxygenation (ECMO) may improve patient outcomes, though it comes with an elevated risk of complications – particularly bleeding and infection – and demands significant resources, posing additional challenges in resource-limited settings. Observational data suggest that venovenous (VV) ECMO may provide life-saving oxygenation in patients with leptospirosis-induced ARDS, particularly in cases complicated by alveolar hemorrhage [7].

In this study, we report a case of a 20-year-old man with severe leptospirosis presenting with AKI associated with respiratory failure unresponsive to optimized mechanical ventilation, necessitating the initiation of daily dialysis and VV ECMO.

2. Case Report

A previously healthy 20-year-old male from northeastern Brazil presented with fever, myalgia, and dry cough that had persisted for two days. One week before admission, he had gone swimming in a lake. Upon admission to an emergency care unit, the patient was hemodynamically stable but exhibited tachycardia and tachypnea.

He initially received oxygen support, followed by non-rebreather mask ventilation. The initial chest X-ray revealed mild diffuse bilateral opacities. Given the epidemiological context of a tropical country, coupled with low platelet counts and AKI with normal potassium levels, leptospirosis was considered the primary diagnosis. Differential diagnoses included dengue, influenza, and bacterial pneumonia. Fungal or viral pneumonia was considered unlikely due to the patient's negative fourth-generation HIV test, lack of immunosuppression history, and no known exposure to histoplasmosis or coccidioidomycosis risk factors. Oseltamivir, ceftriaxone, and azithromycin were promptly initiated. Laboratory results at admission are shown in Table 1.

Table 1. Hematologic and biochemical findings during hospitalization.

Day **Tests in study**	**1st**	**3rd**	**17th**
Hemoglobin, g/dL / Hematocrit, %	9.4 / 28.1	8.3 / 25	9.7
WBCs, /mm3	10,100	25	8,200
Neutrophils, %	92	81	–
Platelets, /mm3	37,000	121,000	160,000
INR	1.39	1.41	–
APTT, ratio	1.33	1.89	–
Sodium, mEq/L	136	140	–
Potassium, mEq/L	3.6	4.3	4.7
Calcium, mEq/L	–	7.81	–
Magnesium, mEq/L	2.1	2.7	–
Urea, mg/dL	72	252	20
Creatinine, mg/dL	3.13	4.17	0.48

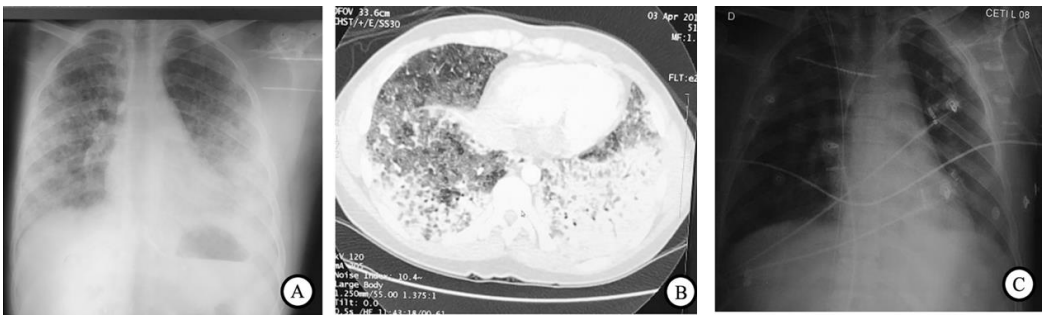
Total bilirubin, mg/dL / Direct bilirubin, mg/dL	0.41 / 0.09	–	–
AST, U/L	58	81	–
ALT, U/L	52	605	–
CK, U/L	233	–	–
LDH, U/L	214	–	–
CRP, mg/dL	15.5	1.4	–
Procalcitonin, ng/dL	0.7	–	–

Abbreviations: ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; CK, creatine kinase; CRP, C-reactive protein; INR, prothrombin-time international normalized ratio; LDH, lactate dehydrogenase; WBCs, white blood cells.

To clarify the diagnosis, nasopharyngeal swab for influenza via real-time polymerase chain reaction (RT-PCR), dengue nonstructural protein 1 antigen and serology tests, leptospirosis serology for immunoglobulin M (IgM) antibodies, microscopic agglutination test (MAT) and RT-PCR for leptospirosis, and blood cultures for pyogenic organisms were requested.

Despite initial respiratory support, the patient's respiratory status worsened. By the third day, his respiratory rate had increased to 52 breaths per minute, and his oxygen saturation had dropped to 39% despite oxygen support. He was using accessory muscles for breathing, and lung auscultation revealed diffuse crackles. Arterial blood gas analysis showed a pH of 7.45, PaO2 of 51 mmHg on a 50% oxygen delivery mask, PaCO2 of 35 mmHg, HCO3- of 24.3 mEq/L, and lactate of 1 mmol/L. A new chest X-ray and computed tomography scan revealed diffuse reticulonodular infiltrates (Figure 1A and 1B). Given his progression to respiratory failure, the patient was intubated and placed on protective mechanical ventilation with a tidal volume of 6 ml/kg. Alveolar recruitment maneuvers were also performed to optimize lung function. Upon aspirating the tube following intubation, a large volume of blood was observed, indicating massive hemoptysis likely due to alveolar hemorrhage.

Figure 1. Imaging studies during hospitalization. **A.** Bedside chest X-ray at intensive care unit admission showed diffuse reticulonodular infiltrates suggestive of acute respiratory distress syndrome. **B.** Chest computed tomography revealed bilateral ground-glass opacities. **C.** Bedside chest X-ray on the day of extracorporeal membrane oxygenation removal showed a significant radiological improvement of the previously observed pulmonary infiltrates.



Despite sedation, analgesia, neuromuscular blockade and optimized mechanical ventilation, the patient developed severe mixed respiratory failure, leading to the decision to initiate VV ECMO. Prone positioning was not attempted due to the suspected massive alveolar hemorrhage and life-threating condition.[8,9] Given the progression, the multidisciplinary team, in consultation with the cardiovascular team, opted for VV ECMO as a

rescue measure, drawing on its success in similar cases of ARDS.[9] During ECMO catheter insertion, the patient experienced a cardiac arrest with pulseless electrical activity secondary to hemorrhagic severe shock, achieving the return of spontaneous circulation after three CPR cycles. He had significant bleeding from the orotracheal tube and puncture sites, requiring multiple transfusions. On the fourth day of hospitalization, dialysis was initiated due to oliguric renal failure, metabolic acidosis and elevated urea levels complicated with bleeding (Table 1). Given the patient's hemodynamic instability and the unavailability of continuous renal replacement therapy, sustained low-efficiency daily dialysis (SLED) was selected as the most appropriate modality.

On the fifth day of ECMO therapy, the patient developed nosocomial pneumonia associated with mechanic ventilation, prompting the addition of piperacillin-tazobactam to cover hospital-acquired pathogens. Later, meropenem and teicoplanin were administered due to the worst of the infectious parameters. Frequent tracheal bleeding led to a reduction in anticoagulation targets with a continuous unfractionated heparin infusion (activated partial thromboplastin time targeted from 50-60 seconds to 40-50 seconds) and, at times, the suspension of anticoagulation. A 3-day course of 250 mg per day methylprednisolone was administered for ADRS, leading to a negative fluid balance and improvements in radiological findings and gas exchange parameters, which enabled ECMO weaning and removal on the eighth day (Figure 1C).

After eight days, ECMO was discontinued due to improvements in respiratory parameters and laboratory markers of infection.

On the sixteenth day of hospitalization, the patient was successfully extubated and transitioned to non-invasive ventilation. Renal function, spontaneous diuresis and urea levels improved, allowing for the discontinuation of dialysis on the seventeenth day (Table 1). By the twenty-sixth day of hospitalization, the patient had fully recovered and was discharged home with no physical or neurological sequalae.
Serological and molecular biology tests returned a negative RT-PCR for Leptospira spp. However, the MAT demonstrated serological conversion, confirming the leptospirosis diagnosis.

3. Discussion

In this case, a previously healthy young male developed fever and myalgia, followed by severe hypoxemic acute respiratory failure seven days after swimming in a lake. His condition was associated with alveolar hemorrhage, thrombocytopenia, and AKI with normal potassium levels. Although other differential diagnoses were considered, leptospirosis was prioritized as the leading diagnosis. His initial symptoms and clinical progression were consistent with known risk factors and the severe clinical presentation typical of leptospirosis [10]. He developed tachypnea and severe hypoxemia secondary to diffuse alveolar hemorrhage, necessitating immediate oxygen supplementation and advanced respiratory support. Despite these interventions, his condition deteriorated, leading to the use of VV ECMO, which resulted in significant improvement and eventual discharge with no sequelae. Notably, the presence of massive alveolar hemorrhage – typically a contraindication for prone positioning – and the life-threatening nature of his condition prompted the timely initiation of ECMO after standard ARDS measures had been exhausted [8, 9].

Given the high morbidity and mortality rates associated with leptospirosis in patients with respiratory involvement, early recognition and treatment are paramount. Pulmonary involvement, characterized by dry cough, chest pain, and dyspnea – with or without hemoptysis or hypoxemia –, typically appears between the fourth and sixth day of illness. It can rapidly progress, potentially leading to mortality within 72 hours [6]. CXRs often reveal abnormalities within the first 24 to 72 hours, aiding in the early diagnosis of febrile syndromes in patients with relevant risk factors. This is particularly important because serological tests for leptospirosis typically become positive only between the sixth and twelfth day of illness. Characteristic radiological findings include nodular lesions that

may be confluent, initially appearing peripherally and later becoming diffusely distributed. These alveolar infiltrates are usually associated with intra-alveolar hemorrhages [10].

Accurate diagnosis of leptospirosis requires a strong clinical suspicion, informed by clinical manifestations and exposure history, since laboratory findings lack specificity, and serological and microbiological tests are time-consuming. In cases of high clinical suspicion, empirical antibiotic therapy with penicillin, doxycycline, or ceftriaxone is recommended [1, 2]. In this case, all molecular tests and microbial cultures were negative, and the diagnosis was confirmed by serological seroconversion.

Severe pulmonary hemorrhagic forms of leptospirosis, particularly those with refractory hypoxemia and resistance to mechanical ventilation, represent a significant challenge in intensive care settings, with high mortality rates. In this instance, the management approach initially involved conventional treatment for ARDS; however, due to its failure and contraindications for certain interventions, VV ECMO and early hemodialysis were initiated. This decision was made despite limited evidence supporting the use of VV ECMO specifically for leptospirosis-related ARDS [8, 9]. ECMO serves as a crucial supportive therapy for severe pulmonary failure refractory to invasive mechanical ventilation by providing extracorporeal gas exchange through venous cannulation and pulmonary bypass. This approach allows for lower mechanical ventilation settings (inspired fraction of oxygen, tidal volume, and driving pressure), which are associated with reduced lung injury and potentially improved outcomes [11, 12].

The primary indication for VV ECMO is severe ARDS that is refractory to conventional treatments, frequently resulting from bacterial, viral, or atypical pneumonia, bronchopulmonary aspiration, acute or chronic interstitial pneumonitis, or barotrauma.[11] A recent individual participant data meta-analysis of randomized controlled trials comparing VV ECMO to conventional mechanical ventilation strategies (high positive end-expiratory pressure, neuromuscular blockade, and prone positioning) in severe ARDS demonstrated improved outcomes in the ECMO group, including lower 90-day mortality, more days alive outside of the ICU, and more days alive without vasopressors, renal replacement therapy, and neurological failure. Notably, the primary causes of ARDS in this study were viral and bacterial pneumonia, sepsis, and pancreatitis. Importantly, the meta-analysis did not mention cases of leptospirosis as an ARDS etiology [13].

VV ECMO facilitates oxygenation and CO2 removal via an extracorporeal circuit, and its usage has increased over the past 15 years due to its promising impact on outcomes [14, 15]. While ECMO can lower mortality and extend ventilator-free, vasopressor-free, and renal replacement-free days, it also carries a heightened risk of bleeding. Additionally, this technology is both invasive and resource-intensive, generally limited to specialized centers due to its high cost and significant healthcare resources. In resource-limited settings, a strategic and selective approach to VV ECMO use could offer essential support, particularly within tertiary centers equipped with sufficient resources and expertise.

Experiences with ECMO for severe pulmonary hemorrhage in leptospirosis are limited to case reports and small case series [16, 17]. These studies suggest ECMO may provide life-saving oxygenation in patients with leptospirosis complicated by ARDS, especially in the instances of alveolar hemorrhage. However, risks such as bleeding and infection seem higher, potentially given the association of leptospirosis with thrombocytopenia and coagulopathy, complicating the use of ECMO, as seen in this case. The current evidence is then limited to support the routine application of VV ECMO for patients with leptospirosis. Nevertheless, given the findings of this recently published meta-analysis, which demonstrated success in treating severe ARDS with VV ECMO, it may be considered as a treatment option depending on the availability of resources and expertise [13]. The decision to initiate ECMO should ultimately be at the discretion of the attending clinician, considering the individual patient's condition and specific circumstances. To our knowledge, this is the first reported case of leptospirosis with respiratory failure managed with VV ECMO in Brazil, a resource-limited country.

There is no consensus on the optimal dialysis modality for leptospirosis. Early initiation of hemodialysis and the use of daily regimens, which help strictly control azotemia and fluid volume, markedly reduce mortality in patients with leptospirosis-induced AKI, particularly those at risk of pulmonary hemorrhage. However, alternate-day hemodialysis is now deemed inadequate for critically ill patients with Weil's disease [18, 19].

4. Conclusion

Therefore, VV ECMO presents a promising option for patients with severe respiratory failure due to ARDS, with a recent meta-analysis showing positive outcomes compared to conventional mechanical ventilation. However, few cases have been reported where leptospirosis was the specific etiology, likely due to the disease being a neglected tropical illness predominantly affecting resource-limited countries. This report presents a successful case of severe ARDS secondary to leptospirosis, managed with VV ECMO and daily dialysis in a resource-limited country, but within a high-level cardiovascular center supported by a multidisciplinary, highly skilled team. In conclusion, despite the limited evidence for the use of VV ECMO in leptospirosis-related ARDS, this therapy warrants further investigation. It may offer potential benefits, especially in regions where leptospirosis remains a significant cause of morbidity and mortality.

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