

Use of Aminocaproic Acid in Combination With Extracorporeal Membrane Oxygenation in a Case of Leptospirosis Pulmonary Hemorrhage Syndrome

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ABSTRACT: A 32-year-old man presented with a 10-day history of fever, chills, nausea, vomiting, myalgia, nonproductive cough, and worsening dyspnea after freshwater swimming in the Caribbean 1 week prior to presentation. Shortly after arrival at the hospital, the patient developed severe respiratory distress with massive hemoptysis. Based on serologic workup, he was diagnosed with leptospirosis pulmonary hemorrhage syndrome leading to diffuse alveolar hemorrhage, severe hypoxemic respiratory failure, and multiorgan failure. He received appropriate antibiotic coverage along with hemodynamic support with norepinephrine and vasopressin, mechanical ventilation, and renal replacement therapy in an intensive care unit. Introduction of extracorporeal membrane oxygenation was initiated to provide lung-protective ventilation supporting the recovery of his pulmonary function. Aminocaproic acid was used to stop and prevent further alveolar hemorrhage. He fully recovered thereafter; however, it is uncertain whether it was the use of aminocaproic acid that led to the resolution of his disease.

KEYWORDS: Leptospirosis, pulmonary hemorrhage, ECMO, aminocaproic acid

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Introduction

Leptospirosis is a spirochetal disease, which does not classically present as Weil syndrome which is rare, but rather as flu-like illness. Pulmonary involvement is present in about 20% to 70% of cases and varies in severity. The leptospirosis pulmonary hemorrhage syndrome (LPHS) has been increasingly recognized as a severe manifestation of the disease with mortality rates surpassing 50%.^{1,2}

Case Report

A previously healthy 32-year-old man started to develop flu-like symptoms 1 day after returning from a Caribbean cruise trip, which stopped in Jamaica, Mexico, and the Cayman Islands. The trip included freshwater swimming at National Park, with no apparent animal contact. His symptoms persisted, and he presented to the hospital after 10 days of fever, chills, nausea, vomiting, myalgia, nonproductive cough, and worsening dyspnea. Physical examination revealed normal vital signs, jaundice, and bilateral conjunctival suffusions. Laboratory workup showed neutrophil-predominant (62%) leukocytosis ($24.6 \times 10^3/\mu\text{L}$), thrombocytopenia ($78 \times 10^3/\mu\text{L}$), creatinine level of 5.29 mg/dL, aspartate transaminase of 736 U/L, alanine transaminase of 495 U/L, and markedly elevated levels of

direct bilirubin (17.8 mg/dL) and creatine kinase (2426 U/L). The initial chest x-ray (CXR) was unremarkable.

He was initially admitted to the regular floor, but 1 day after admission, he developed worsening multiorgan dysfunction and episodic hypotension requiring intensive care unit admission. After 36 h of arrival, the patient developed massive hemoptysis and acute hypoxemic respiratory failure, leading to acute respiratory distress syndrome. He received hemodynamic support with norepinephrine and vasopressin, mechanical ventilation, and renal replacement therapy.

There was a high clinical suspicion for severe leptospirosis, based on his history of exposures, and the clinical presentation of liver failure, pulmonary hemorrhage, and neutrophil-predominant leukocytosis in a relevant time frame. He was therefore started on ceftriaxone and doxycycline. Leptospirosis indirect hemagglutination assay eventually yielded positive results, and the patient completed a 14-day course of doxycycline and 7 days of ceftriaxone.

Repeat CXR revealed extensive bilateral pulmonary infiltrates, $\text{Pao}_2/\text{Fio}_2$ ratio (P/F) remained below 30 mm Hg, and plateau pressures remained above 40 cm H_2O despite optimized ventilator support, deep sedation, and paralysis. At that point,



the decision was made to start veno-venous extracorporeal membrane oxygenation (VV-ECMO) to facilitate gas exchange. Patient was cannulated in a femoral-femoral approach, and VV-ECMO was introduced without complications. Oxygen saturation prior to VV-ECMO initiation ranged from 74% to 80%, improving to 98% to 100% within minutes after ECMO initiation. Consequently, P/F ratio continued to improve dramatically, allowing for a lung-protective ventilation strategy.

Hemoptysis persisted during VV-ECMO despite an adjusted heparin protocol with a target activated clotting time (ACT) range of 160 to 180 seconds (standard ECMO regimen dictates an ACT range: 180-220 seconds), requiring the use of a significant amount of blood products. To stop and prevent further alveolar hemorrhage, and based on previous studies on ECMO patients, initiation of continuous aminocaproic acid infusion at 20 mL/h was tried after about 13 days on ECMO for a duration of 6 days, which presumably resulted in improved lung aeration and significantly decreased transfusion requirements. Due to persistent thrombocytopenia, he required multiple platelet transfusions to maintain a count of about 60 to $120 \times 10^3/\mu\text{L}$. The last unit of platelets was given about 15 days after presentation, around the same time of ECMO discontinuation, which coincides with his clinical improvement.

Veno-venous extracorporeal membrane oxygenation was discontinued after 18 days of therapy. The patient was extubated and discharged home to continue with outpatient rehabilitation after a 40-day hospitalization. He achieved a complete recovery and had evidence of normal pulmonary function tests at 6-month follow-up.

Discussion

Patients with LPHS may develop significant hypoxemia requiring mechanical ventilation. The use of ECMO has been increasingly recognized as an alternative for cases in which hypoxemia persists despite the use of high FiO_2 and positive end-expiratory pressure (PEEP).^{3,4} Using an extracorporeal circuit for gas exchange, ECMO allows a ventilation strategy with lower tidal volumes, FiO_2 , and PEEP, which in turn decreases the rate of ventilator-associated lung injury.⁵

Conditions which hinder the use of systemic anticoagulation are considered relative contraindications to the use of ECMO given the increased risk of in-circuit thrombosis. Nonetheless, cases describing the use of ECMO in patients with diffuse alveolar hemorrhage (DAH) have been reported.⁶⁻¹¹ Furthermore, strategies described to prevent further hemorrhage in patients with active bleeding while on ECMO include the use of fresh-frozen plasma, vitamin K, aprotinin, and recombinant activated factor VII, as well as avoiding the concomitant use of heparin and using only nafamostat mesilate as a regional anticoagulant.¹²⁻¹⁴

Aminocaproic acid is a lysine analogue effective in certain bleeding disorders due to its inhibitor effect on plasmin. Despite the theoretical risk of in-circuit thrombosis, retrospective

studies indicate that its use is safe in patients on ECMO who develop life-threatening hemorrhage.¹⁵ Nevertheless, experience with the use of aminocaproic acid in patients with DAH who are on ECMO remains limited.⁷

To the best of our knowledge, this is the first report of continuous aminocaproic acid infusion along with an adjusted heparin protocol to stop and prevent further alveolar hemorrhage in a patient on ECMO in the setting of LPHS. Another case report by Liao et al¹⁶ describes a patient with severe leptospirosis complicated by massive pulmonary hemorrhage, who was managed successfully with ECMO for resistant hypoxemic respiratory failure for 6 days; compared with our patient, the duration of ECMO was much less and there was no apparent need of prothrombotic therapy to help manage the active bleed.

Whether aminocaproic acid led to the improvement of our patient or there was spontaneous improvement remains unclear. Unfortunately, besides ACT, fibrinogen, complete blood counts, and coagulation studies, there was no follow-up of other hematologic laboratory values, such as thromboelastography analysis, to determine the specific role of aminocaproic acid in our patient. However, indirect measures such as symptomatic improvement and a significant decrease in blood product requirement suggest a beneficial effect.

Possibly not in the setting of a severe infection, such as a patient with leptospirosis and pulmonary hemorrhage, there are several studies on the use of ECMO and aminocaproic acid with and without steroids in stem cell transplant patients with DAH. The role of aminocaproic acid is still controversial regarding improvement in clinical outcomes.¹⁷⁻¹⁹

Aminocaproic acid has also been more studied in pediatric patients on ECMO complicated by bleeding.^{15,20,21} Prospective studies are needed to confirm the safety and efficacy of aminocaproic acid to stop and prevent further alveolar hemorrhage in adult patients undergoing ECMO. As evidenced by this clinical case, leptospirosis can be life-threatening in its most severe forms, and the most prevalent areas should increase awareness to the general public regarding recreational, occupational, or household exposures that could potentially cause disease transmission.

Author Contributions

MP and RM contributed equally to this manuscript. This work was performed at the University of Miami Miller School of Medicine and Jackson Memorial Hospital.

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