

Leptospirosis-associated catastrophic respiratory failure supported by extracorporeal membrane oxygenation

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Abstract A previously healthy, 39-year-old obese farmer, arrived hypotensive and tachycardic, with fever, myalgia, headache, abdominal pain, diarrhea, and progressive dyspnea. Ten days before symptoms onset, he was in direct contact with mice and working in a contaminated drain. Patient laboratory showed acute kidney injury and thrombocytopenia. Chest X-ray exhibited bilateral diffuse interstitial infiltrates. First-line empirical antibiotics were started and influenza discarded. Patient evolved with severe respiratory failure, associated with hemoptysis, and rapidly severe hemodynamic compromise. Despite neuromuscular blockade and prone positioning, respiratory failure increased. Accordingly, veno-venous ECMO was initiated, with bilateral femoral extraction and jugular return. After ECMO connection, there was no significant improvement in oxygenation, and low pre-membrane saturations and low arterial PaO₂ of the membrane showed that we were out of the limits of the rated flow. Thus, a second membrane oxygenator was installed in parallel. Afterward, oxygenation improved, with subsequent perfusion enhancement. Regarding etiology, due to high suspicion index, *Leptospira* serology was performed, coming back positive and meropenem was maintained. The patient ultimately recovered and experience excellent outcome. The clinical relevance of the case is the scared

evidence of leptospirosis-associated severe respiratory failure treated with ECMO. This experience emphasizes the importance of an optimal support, which requires enough membrane surface and flow for an obese, highly hyperdynamic patient, during this reversible disease. A high index of suspicion is needed for an adequate diagnosis of leptospirosis to implement the correct treatment, particularly in the association of respiratory failure, pulmonary hemorrhage, and an epidemiological-related context.

Keywords *Leptospira* · Extracorporeal membrane oxygenation · Respiratory failure

Introduction

Leptospirosis is a zoonosis caused by pathogenic spirochetes of the genus *Leptospira* that typically occurs in tropical and temperate regions. The global incidence is not well established, but the World Health Organization estimates that there are 873,000 cases per year in the world, causing with 48,600 deaths [1]. Although its incidence rate is increasing, with multiple outbreaks and significant morbidity, it remains an elusive diagnosis [2]. It is under national surveillance in Chile since 2002, but the scarce number of cases per year is probably explained because of underdiagnoses.

Leptospira infects both wild and domestic mammals—rodents, cows, and dogs, among others, but rodents are the most important vectors [3]. Infection is acquired via direct patient skin or mucosa contact with infected animals; or indirectly, through contact with contaminated urine (environmental contamination, particularly in stagnant water) [4]. Exposure is common among farmers and septic drain clean up crews. Symptoms usually begin 1 or 2 weeks after infection, and are characterized by fever accompanied by a broad

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spectrum of flu-like symptoms that can lead to extensive tissue damage, vasculitis, and multiorgan failure (Table 1). Most cases are mild and self-limited, although some are serious and potentially fatal.

A high index of suspicion is required for diagnosis, based mainly in epidemiological data of exposure and the previously described symptoms. Since clinical and laboratory findings are non-specific, serological test is needed for diagnostic confirmation. Culture and molecular diagnosis are available in some reference laboratories only.

Table 1 Signs and symptoms

Symptoms	Signs
Fever	100%
Headache	99%
Myalgias	71%
Nausea/vomiting	64%
Abdominal pain	48%
Constipation	35%
Diarrhea	17%
Cough	23%

Reference [26]

Case

Previously healthy, 39-year-old (120 kg and 180 cm) obese farmer, arrived at the Emergency Department (ED) with fever, retro-orbital headache, and intense muscular pain. On interrogation, 10 days before symptom onset, he was in direct contact with mice and working in a contaminated drain. After initial evaluation, he receives symptomatic treatment and was discharged.

He evolved with abdominal pain, vomiting, diarrhea and dyspnea, reason why he consults at the ED 72 h later. On admission, he was hypotensive, tachycardic, non-febrile, with 96% pulse oximetry saturation breathing room air. Chest X-ray showed bilateral diffuse interstitial infiltrates. Initial laboratory findings are presented in Table 2. Due to local Chilean epidemiology, rapid test for Hantavirus and influenza A and B were performed, which were negative for these pathogens. With presumptive diagnosis of multiorgan dysfunction due to septic shock secondary to interstitial pneumonia, he was admitted the ICU. First-line empirical antibiotics were started (ceftriaxone and metronidazole).

During the following hours, severe dyspnea, with progressive oxygen requirement and hemoptysis ensued. He was intubated, sedated, and protective invasive mechanical ventilation initiated. Rapidly severe hemodynamic compromise

Table 2 Patient's blood count, biochemistry and inflammatory parameters evolution

Days	- 1	1	2	3	4	5	6	7	8	9
Hemoglobin (g/dL)	12.9	9.2	11.8	10.6	10.3	8.9	9.2	8.6	8.3	7.5
White blood cells count (mm ³)	7.1	8.67	13.8	15.07	18.37	17.52	18.26	13.32	9.72	7.71
Band (%)		12	11	20	19	10	8	10	9	9
Lymphocytes (%)		6	11	11	13	7	6	6	10	8
Platelet count (mm ³)		26	62	44	62	77	110	121	158	206
Prothrombin time (%)	67	13.2	13	12.3	11.2		10.6	10.3	10.1	10.5
INR	1.24	1.19	1.17	1.11	1.02		0.96	0.94	0.92	0.95
aPTT (s)	32.9	31.1	23.7	23.3	24.6	26.4	30.01	32.6	34.1	62.5
Albumin (gr/dL)		2.8		2.9		3.4		3.5	3.5	
Lactic Dehydrogenase (U/L)		363	527	437	469	463	484	537	641	598
Blood ureic nitrogen (mg/dL)	72	52	52	46	43	42	48	36	35	48
Creatinine (mg/dL)	5	3.22	2.58	2.14	2.04	2.09	2.77	2.06	2	2.45
Total bilirubin (mg/dL)	2.1	6.6	7.3	5.5	7.6	7.6	7.7	6.6	5.9	4.7
Direct bilirubin (mg/dL)	1.4	6.5	7.2		7.1	7.3	5.9		5.4	4.1
GOT (U/L)	105	99		83	83	85	110	119	126	109
GPT (U/L)	83	65			52		63	64	68	62
GGT (U/L)	157	73			80		186		178	151
Lactic acid (mg/dL)	12	11	16.2	11			12	7	7	8
C-reactive protein (mg/dL)	315	281			81		89	115	125	110
Procalcitonin (ng/mL)		53.59	52.77						5.1	
SOFA		21	17	18	16	16	16	14	11	11

INR international normalized ratio, aPTT activated partial thromboplastin time, GOT glutamate oxaloacetate transaminase, GPT glutamic-pyruvic transaminase, GGT gamma-glutamyltranspeptidase, SOFA sequential organ failure assessment

presented (noradrenaline requirement up to 0.4 mcg/kg/min and adrenaline up to 0.25 mcg/kg/min). In addition, oxygenation parameters dropped to a PaO₂:FiO₂ ratio (Pa/FiO₂) of 131; leading to neuromuscular blockade initiation and PEEP adjustments. Control laboratory parameters are shown in Table 2. At this point, due to progressive respiratory failure, transferred was requested to a center with ECMO availability, thus being transferred to our hospital.

Upon admission, the patient exhibited severe hemodynamic instability with high vasoactive drug requirements, catastrophic respiratory failure, with a Pa/FiO₂ ratio of 89, and oliguric renal failure. Calculated APACHE II score was 23. Initial bedside echocardiography was suggestive of hypovolemia, with no right cavities dilatation and good left ventricle contractility. Pulmonary imaging showed diffuse bilateral opacities (Fig. 1). Preload was optimized, profound sedation and neuromuscular blockade were adjusted, and high-volume hemofiltration (HVHF) was initiated, with a good clinical response associated with a 60% reduction in vasoactive drugs. Admission blood cultures, bronchial secretion, and urine cultures came back negative, but Herpes Simplex virus type I was detected on respiratory tract, interpreted as an epiphenomenon. HIV and repeated Hantavirus serology were negative. Due to profound septic shock and considering its catastrophic course, empirical second-line antibiotics were started (meropenem, vancomycin, amikacin, plus iv. acyclovir).

An initial good respiratory and hemodynamic response was observed for 24 h; however, after one episode of hemoptysis, abrupt deterioration in gas exchange, mainly oxygenation, ensued. Prone maneuver was attempted, but Pa/

FiO₂ ratio remained below 80 with a Murray score of 3. Accordingly, veno-venous ECMO was initiated, with bilateral femoral extraction (29F and 21F) and jugular return (21F). A Euroset polymethylpentene oxygenator was used.

After ECMO connection, there was not a significant improvement in oxygenation, although all usual parameters were optimized. Low pre-membrane saturations and low arterial PaO₂ of the membrane showed that we were out of the limits of the rated flow. Thus, a second membrane oxygenator was installed (in parallel—Fig. 2). Afterward, oxygenation improved, with subsequent perfusion enhancement, evidenced by a positive lactate clearance. A second bedside echocardiography showed a drop in left ventricular ejection fraction, but without pulmonary hypertension, and it was interpreted as septic/hypoxic cardiomyopathy.

On the following days, several transfusions were required due to anemia and thrombocytopenia, and numerous bronchoscopies were also necessary for airway clots toilette. Alteration on hepatic laboratory values was initially interpreted as septic shock hepatitis.

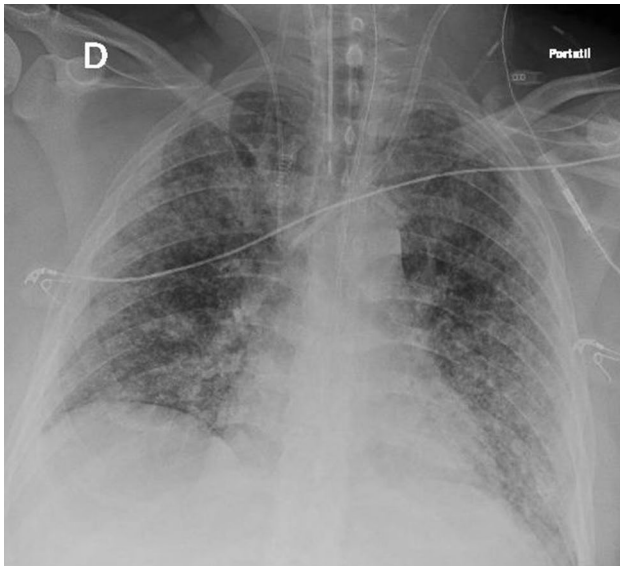


Fig. 1 Pre-ECMO chest X-ray showing pulmonary diffuse bilateral opacities in the context of leptospirosis



Fig. 2 ECMO setup for the patient: double oxygenator in parallel

Regarding etiology, due to high suspicion index, Leptospira serology was performed, coming back positive; thus, meropenem was maintained. Acyclovir therapy was administered for 10 days. During his evolution, a tracheobronchitis due to resistant *Klebsiella oxytoca* was treated, and an important epistaxis required posterior tamponade for 2 days, both pathologies resolved without further complications. Uveitis was discarded by ophthalmologic evaluation.

Initially, high ECMO flows were necessary, up to 8 L with 2 oxygenators, without evidence of mechanical complications. Progressive improvement in pulmonary function and images (Fig. 3) allowed for ECMO withdrawal on day 8. Afterward, pseudoaneurism of the right femoral artery, which was not cannulated, became evident, and was surgically repaired without complications. The patient was

discharged home on day 28, completely recovered and with no sequelae.

Discussion

Leptospirosis can present with a wide range of symptoms, mimicking flu, hepatitis, dengue, hanta virus cardiopulmonary syndrome, meningitis, among others, and has a specific treatment; thus, clinical suspicion must remain high and serological diagnosis should be performed. In Chile, hanta virus [5] and Influenza are the most common differential diagnosis of patients presenting with flu-like symptoms and respiratory failure in the right epidemiological setting.

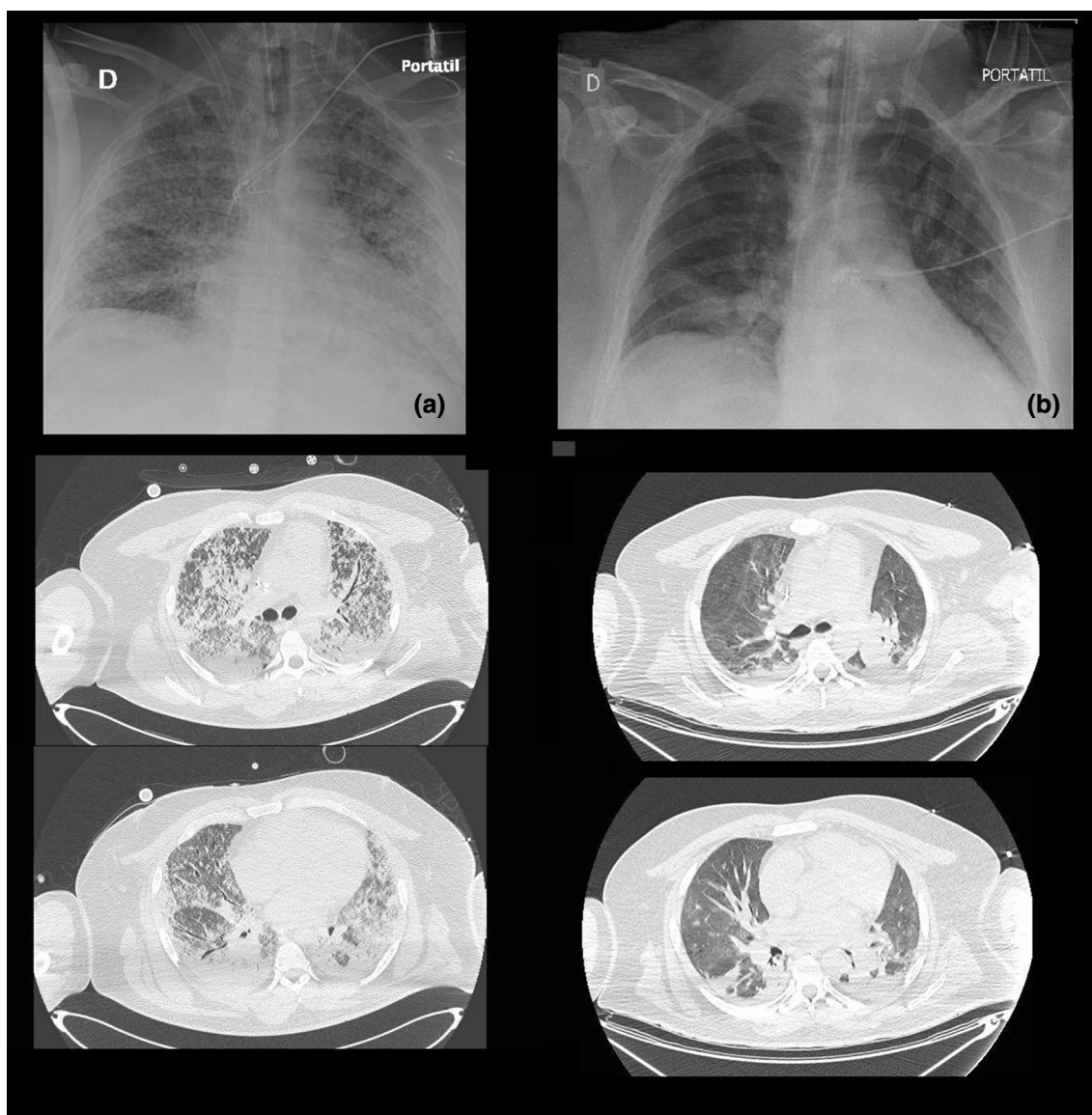


Fig. 3 Chest X-ray and CT evolution of the patients **a** before and **b** after ECMO

Classic manifestations of leptospirosis are mainly due to its pathogenic mechanism, in which a bacterial glycoprotein acts as endotoxin and perforates cell membranes [6]. Later, via hematogenous dissemination, small blood vessel vasculitis can develop [6, 7]. Due to its multi-systemic involvement, severe disease can exhibit a wide variety of signs and symptoms. Among these, our patient presented with hepatitis, acute kidney injury, acute respiratory distress syndrome (ARDS), pulmonary hemorrhage, which is present in up to 3.7% of cases [8], myocarditis, and rhabdomyolysis. The most severe clinical form of leptospirosis is known as Weil’s disease, which is uncommon (5–10% of cases), and is characterized by hepatic, renal, and pulmonary involvement [7–11]. Other possible complications, not presented in our patient, include lymphocytic meningitis, and uveitis [12–14]. Characteristic associated vasculitis of the severe form of the disease can be extremely severe, in some cases leading to limb necrosis [15].

Acute kidney injury is due to tubular-interstitial nephritis and is often non-oliguric, and only sometimes requires renal replacement therapy. Among survivors, renal function commonly recovers [16–18]. In the presented case, intermittent high-volume hemofiltration was used in the setting of profound shock to decrease vasoplegia intensity.

Leptospirosis mortality rates in hospitalized patients range from 4 to 52% [19]. Pulmonary and central nervous system involvement are described as predictors of mortality. In the case of pulmonary involvement, mortality rises to 71%

[20]. Other series also suggest that jaundice, renal failure, and an age above 60 are mortality risk factors [21, 22]. In one series of cases, 52% of the patients present with specific organ involvement, with the other 48% of cases presenting with only a non-specific febrile syndrome [22, 23].

Many antibiotics are effective for leptospirosis, including penicillin, 3rd generation cephalosporins, carbapenems, macrolides, and tetracyclines. In severe presentations, supportive therapies are essential for survival, considering that multiorgan failure (MOF) is typically completely reversible [24]. Veno-venous ECMO provides immediate support of oxygenation and ventilation and helps ensure protective ventilation without further compromising oxygen delivery nor acid base balance [25]. In the case presented, profound septic shock, with MOF and catastrophic ARDS, made it impossible to ventilate the patient protectively and simultaneously supply adequate oxygenation and ventilation; thus, ECMO was initiated.

ECMO is increasingly being used for this type of patients with severe ARDS, but it is important to understand ECMO physiology, in particular in obese and hyperdynamic patients, such as the presented case [26]. This obese patient, with a body surface area of 2.3–2.4 m² and an estimate required cardiac index of at least 4 L/min/m², needs approximately 9 to 10 L min of oxygenated cardiac output. Initially, with only one oxygenator, ECMO flow was 6.6 L min, with a fully oxygenated blood (PaO₂ after oxygenator of 105 mmHg); accordingly, even with no recirculation, this

Table 3 Patient arterial and post oxygenator’s blood gas evolution

	Day 1	Day 2	2 h pre-ECMO	1 h post-ECMO	1 h post-second oxygenator	Day 3*	Day 4	Day 6	Day 8	Day 10
Patient FiO ₂	0.5	0.5	1	1	1					
Patient paCO ₂	38.7	40	65.9	53.8	34.5	50	44.9	49.3	35.6	35.5
Patient paO ₂	82.1	79	77	34.5	39	76	74.1	68	85.8	103.1
Patient pH	7.36	7.39	7.18	7.2	7.38					
Patient lactate (mmol/L)	10	11	21	44	35			12	7	10
Patient SvO ₂ (%)	77	74	83	56	71			82	77	
Patient venous PCO ₂	47	48	75	54	34			36.6	46	
Patient Hematocrit (%)	32	27	25.3	28	34.5	29.7	31.9	26.6	25.9	23
ECMO flow (L/min)	–	–	–	6.6	8	7.5	7	6.5	5.5	3
ECMO fresh gas flow (L)	–	–	–	11	8	10	10	6	2	1
ECMO negative pressure	–	–	–	– 80	– 78	– 75	– 70	– 50	– 45	– 40
Ox1 pCO ₂	–	–	–	43.3	–	28.6	31.6	28.7	41.3	29.2
Ox1 pO ₂	–	–	–	105	–	410	408	449	340	258
Ox2 pCO ₂	–	–	–	–	28.6	27	34.7	28.9	40	38.7
Ox2 pO ₂	–	–	–	–	410.1	270	363	375	385	294

paCO₂ carbon dioxide partial pressure in patient’s arterial blood gas (mmHg), paO₂ oxygen partial pressure in patient’s arterial blood gas (mmHg), ECMO negative pressure: circuit pressure before pump (mmHg), Day 3* 12 h post-second oxygenator; Ox1/2 pCO₂ carbon dioxide partial pressure in post oxygenator’s blood gas (mmHg), Ox1/2 pO₂ oxygen partial pressure in post oxygenator’s blood gas (mmHg)

flow was insufficient to meet patient requirements. The addition of a second oxygenator allow us to increase oxygenated blood flow to 8 L/min, increasing oxygen delivery, and better meet patient oxygen demands (Table 3). In parallel we try to decrease oxygen consumption by decreasing the patient hyperdynamic state with high flow hemofiltration and temperature management. The need of double oxygenators in veno-venous ECMO is not frequently reported [27], but it could be highly useful as a strategy to reach adequate oxygen delivery (DO_2) to surpass the patient VO_2 , thus stopping the oxygen debt and the shock vicious cycle.

Conclusion

To our knowledge, this is one of the few cases that describes the need of ECMO in Weil disease, and in addition, with a good outcome [28, 29]. All cases have in common the presence of pulmonary hemorrhage as a cause of pulmonary insufficiency, as is our case. A high index of suspicion, combined with the appropriated supportive therapy, was essential for patient survival.

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