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Case report

Leptospirosis manifested with severe pulmonary haemorrhagic syndrome successfully treated with venovenous extracorporeal membrane oxygenation

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SUMMARY

Leptospirosis, one of the most important of neglected tropical diseases, is a common zoonosis in the tropics. Recent reports have demonstrated that pulmonary haemorrhage is one of the fatal complications of severe leptospirosis. In this report, we present a case of leptospirosis manifested with severe pulmonary haemorrhagic syndrome successfully treated with venovenous extracorporeal membrane oxygenation (VV-ECMO). A 39-year-old man who lives in Bangkok presented with fever, severe myalgia and haemoptysis. With rapid progression of acute respiratory failure in 6 hours, he was intubated and a litre of fresh blood was suctioned. Chest x-ray showed diffuse alveolar infiltrates compatible with ARDS, then mechanical ventilator with lung protective strategy was used. Diagnosis of leptospirosis with diffuse alveolar haemorrhage was made. Refractory hypoxaemia was not responsive to positive end-expiratory pressure (PEEP); thus, VV-ECMO was initiated on the first day. Other treatments included plasmapheresis, intravenous pulse methylprednisolone and intravenous antibiotics. The outcome of treatment was successful, and this patient was discharged to home on day 14 after admission.

BACKGROUND

Leptospirosis is a widespread zoonosis caused by pathogenic spirochetes of the genus *Leptospira*, transmitted to humans through contaminated water or soil or directly exposed to the infected urine of carrier mammals. Leptospirosis is mainly take place in the rural area during the rainy season, much more prevalent than in the big city. Leptospiral infection is associated with an excessively broad spectrum of severity ranging from subclinical illness to two clinical syndromes. First, the anicteric form is typically a mild illness that accounts for 90%–95% of cases. Clinical symptoms include fever, myalgia, headaches, conjunctival suffusion and mild gastrointestinal symptoms that can be resolved spontaneously. The other 5%–10% is the more severe icterohaemorrhagic form (or Weil's disease, first reported in 1886). In the latter group, patients typically have hepatic and renal failure.¹ Alteration of consciousness, haemorrhagic diathesis, pneumonia and respiratory failure may also appear. Pulmonary involvement in leptospirosis was found up to 20%–70% ranging from a cough, dyspnoea,

haemoptysis to acute respiratory distress syndrome (ARDS).^{2,3} Pulmonary haemorrhage in leptospirosis is associated with high mortality. Only a few cases successfully treated with extracorporeal membrane oxygenation (ECMO) have been reported. We hereby presented a case of leptospirosis manifested with severe pulmonary haemorrhagic syndrome with successfully treated with venovenous extracorporeal membrane oxygenation (VV-ECMO).

CASE PRESENTATION

A 39-year-old Thai man, a street vendor who lives in Bangkok, presented to the emergency department with a 5-day fever and myalgia. Six hours before coming to the hospital, he developed breathlessness and haemoptysis. He had no medical history of note, but 20-pack-year smoking. Physical examination revealed high body temperature (39.8°C) and tachypnea with signs of respiratory distress, no conjunctival suffusion and no icteric sclera.

INVESTIGATIONS

Chest radiography showed a bilateral, diffuse opacification pattern (figure 1). Arterial blood gas at room air revealed a pH of 7.42, pCO₂ of 35.7 mm Hg, pO₂ of 55 mm Hg, SpO₂ 89%, lactate 1.2 with FiO₂ of 1.0. Laboratory investigation revealed a normal complete blood count (haemoglobin 108 g/L, mean corpuscular volume 93 fL, platelet 117,000, white blood cell count 10 250, neutrophil 89.9%, lymphocyte 5.4%, monocyte 4.4%, eosinophil 0%, basophil 0.3%), mild degree of coagulopathy (prothrombin time (PT) 13.7 (normal 9.8–12.8), international normalized ratio (INR) 1.23, activated partial thromboplastin time (aPTT) 29.3 (normal 21.9–31.1)), total bilirubin 1.51 mg/dL (normal 0.2 to 1.2), alanine aminotransferase 48 U/L (normal 0–40), creatinine 0.93 mg/dL (normal 0.7–1.2) and albumin 3.4 g/dL (normal 3.5–5.0). Urinalysis showed mild proteinuria (2+), microscopic haematuria (red blood cell count 20–30 cells/HPF). The Thai-Lepto score was 8.5 points.

After intubation, a litre of fresh blood was suctioned via the endotracheal tube. The patient was admitted at the intensive care unit with an Acute Physiology and Chronic Health Evaluation (APACHE) II score 17 and developed respiratory distress with oxygen desaturation.

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Figure 1 (A) Chest X-ray of the patient on day 1 before VV-ECMO. (B) Chest X-ray of the patient on day 1 after VV-ECMO. (C) Chest X-ray of the patient on day 2. (D) Chest X-ray of the patient on day 3. (E) Chest X-ray of the patient on day 5. (F) Chest X-ray of the patient on day 10. VV-ECMO, venovenous extracorporeal membrane oxygenation.

DIFFERENTIAL DIAGNOSIS

The patient was presumptively diagnosed with diffuse alveolar haemorrhage (DAH) with severe ARDS. Differential diagnosis is small vessel vasculitis and infectious disease-associated DAH, such as influenza A, dengue, leptospirosis, malaria, *Staphylococcus aureus* infection.⁴ The patient was placed on ventilator support with a lung-protective strategy. Sedations and neuromuscular blockade were adjusted with cisatracurium 10 mg/hour (3 mcg/kg/min), propofol 150 mg/hour, midazolam 10 mg/hour and fentanyl 100 mcg/hour (1.81 mcg/kg/hour), and treated with ceftriaxone 2 g intravenously every 24 hours and levofloxacin 750 mg intravenously once daily as severe community acquired pneumonia (figure 2). At 2 hours after admission, plasmapheresis was initiated and then continued for 5 days. Intravenous pulse methylprednisolone (IVMP) 250 mg was administered intravenously every 6 hours in the first 2 days, with a total of five doses after all serological tests of vasculitis, including cytoplasmic type and perinuclear type of anti-neutrophil cytoplasmic antibodies (cANCA, pANCA), anti-myeloperoxidase (anti-MPO), anti-proteinase 3 (anti-PR3) and anti-glomerular basement membrane (anti-GBM) antibodies showed negative result.

Figure 2 Clinical course of the patient. Bar chart demonstrates ECMO flow (L/min); red line shows PaO₂; green line shows creatinine, yellow line shows bilirubin. ECMO, extracorporeal membrane oxygenation; IVMP, Intravenous pulse methylprednisolone.

Treatment

At admission for 12 hours, severe hypoxaemia and hypercapnia progressively worsed; the mechanical ventilator mode was adjusted to PCV mode, inspired pressure of 20 cmH₂O, respiratory rate of 30 per min, PEEP of 20 cmH₂O, FiO₂ of 1.0, but arterial blood gas showed pH 7.128, paO₂ of 74.2 mm Hg and paCO₂ of 89.3 mm Hg. VV-ECMO was started via the left femoral vein for access and via the right internal jugular vein for return. In the beginning, VV-ECMO setting was at a blood flow rate of 4.0 L/min, with sweep gas flow through the oxygenator at 4.0 L/min of 100% oxygen. Then the mechanical ventilator was set as volume-controlled mode, tidal volume of 220 mL (4 mL/kg), respiratory rate of 8 breaths/min, PEEP of 10 cmH₂O and FiO₂ of 0.3.

The leptospirosis diagnosis, in this case, was confirmed by leptospiral DNA detection in blood by PCR (Lip132-PCR) returned 24 hours after the admission. Anti-*Leptospira* IgM antibodies were negative at the first day of admission (the fifth day of symptom) and positive, 28.364 Panbio unit (<9=negative, 9–11=gray zone and >11=positive), at the eighth day of admission (the 12th of symptoms).

Transthoracic echocardiography revealed a normal left ventricular size and its systolic function (left ventricular ejection fraction (LVEF) = 60% by Teichholz method) and no evidence of vegetation. Haemoculture was negative. Sputum culture was negative. Sputum acid-fast bacilli and modified acid-fast bacilli were negative. Anti-HIV was negative. Anti-hepatitis C virus was negative. HBsAg, anti-HBs, anti-HBc were negative. Weil-Felix test, OX 19 titre, OX K titre and OX 2 titre were negative. Scrub typhus Ab and Murine typhus Ab IgG and IgM were negative. The serum dengue NS1 antigen and IgM were negative, while dengue IgG was positive. The influenza A/B/respiratory syncytial virus (RSV) rapid test and reverse transcription polymerase chain reaction (RT-PCR) were negative. Respiratory virus 19 subtypes were negative. Thin and thick blood films for malaria were not found. Antinuclear antibodies (ANA) was negative. CH50 was 44.9 U/mL (42–95), C3 138 mg/dL (76–171) and C4 53.4 mg/dL (10–40).

OUTCOME AND FOLLOW-UP

During the deterioration of his respiratory condition, the renal function was slightly impaired and returned to normal in the fourth day of admission without renal replacement therapy. Also, liver function test was generally normal.

His condition improved. The patient was weaned off VV-ECMO on the fifth day of admission and there was withdrawal of VV-ECMO and endotracheal tube on day 8, and day 10 subsequently. Haemodynamic parameter and ECMO setting are shown in table 1 and figure 2. The patient was discharged from the intensive care unit with stable condition, good consciousness and no dyspnoea on the 10th day of admission. He was discharged home on day 14 after admission. After 1 year follow-up, the patient recovered and became healthy again.

DISCUSSION

In the present report, we report a case of severe leptospirosis which manifested with DAH with severe hypoxaemia refractory to conventional respiratory support. His life-threatening condition was successfully supported by using VV-ECMO. His condition markedly improved and he was discharged on day 14 of admission.

This present case is a food vendor who lives in Bangkok metropolitan region. Leptospirosis has latterly emerged as an

Table 1 Review of the case report: leptospirosis with pulmonary haemorrhage																
	Arokianathan <i>et al</i> ²⁰		Assimakopoulos <i>et al</i> ³¹		Kahn <i>et al</i> ³²		Liao <i>et al</i> ³³		Ludwig <i>et al</i> ³⁴		Cantwell <i>et al</i> ³⁵		Umei <i>et al</i> ³⁶		Jukkaphop C <i>et al</i> (this case)	
Age (year)	30	30	28	57	80	58	N/A	32	34	39	50	39	50	39	Male	
Gender	Male	Male	Male	Male	Male	Male	Male	Male	Male	Male	Male	Male	Male	Male	Male	
Comorbidity	None	None	None	None	HT, AF, T2DM, HF	Ulcerative colitis, T2DM	N/A	None	None	Obesity	None	None	None	None	None	
Presentation	4 days of myalgia, jaundice	2 days of fever, headache, dyspnoea and haemoptysis	10 days of fever, haemoptysis, jaundice, AKI	2 days of fever, myalgia, haemoptysis and AKI	4 days of fever, myalgias, non-bloody diarrhoea and AKI	Flu-like symptom	2 days of fever, myalgia and jaundice	7 days of fatigue and vomiting, and presentation with dyspnoea, jaundice and AKI	2 days of fever, myalgia, progressive dyspnoea and AKI	2 days of fever, myalgia and jaundice	5 days of fever, myalgia; 6 hours of dyspnoea and haemoptysis					
Haemoptysis	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	
PaO ₂ /FIO ₂ ratio	N/A	210	200	90	150	N/A	163	N/A	N/A	131	70	74.2	70	74.2	74.2	
Treatment	MV MARS	MV	MV RRT	MV RRT	MV RRT	MV RRT	MV RRT	MV RRT	MV Plasmapheresis RRT	MV Plasmapheresis RRT	MV RRT	MV Plasmapheresis RRT	MV RRT	MV Plasmapheresis RRT	MV Plasmapheresis	
ECMO Initiate day	VV-ECMO 183 hours	Not done	Not done	Not done	Not done	VA-ECMO 60 hours	VV-ECMO, 1 day and total of 6 days	VV-ECMO, 1 day	VV-ECMO, 2 days after admission, double membrane oxygenator, in parallel	VV-ECMO, 3 days after admission, (day 5 after symptom)	VV-ECMO, 12 hours and total of 8 days					
Outcome	Improved	Improved	Improved	Improved	Dead (multiorgan failure)	Improved	Improved	Dead, 29 hours after initial presentation (multiorgan failure)	Improved	Improved	Improved	Improved	Improved	Improved	Improved	
AF, atrial fibrillation; AKI, acute kidney injury; ECMO, extracorporeal membrane oxygenation; HF, heart failure; HT, hypertension; MARS, molecular adsorbent recirculating system; MV, mechanical ventilator; N/A, not available; RRT, renal replacement therapy; T2DM, type 2 diabetes mellitus; VA-ECMO, veno-arterial extracorporeal membrane oxygenation.																

important urban health issue caused in the developing country due to the rapid and disorganised expansion of urban centres, which turn out to be a suitable ecological condition for rat-borne transmission. Because of insufficient evidence, as our data analysis, Bangkok metropolitan region rarely found pathogenic *Leptospira* in floodwater samples, and the number of human leptospirosis cases reported was relatively low.⁵ High incidence of the disease was found in agricultural regions related with animal farming and rural subsistence.^{5,6} Leptospirosis in urban case is quite difficult to diagnose; therefore, recognition of this disease is necessary. Leptospirosis should be considered by physicians when patients present with fever, sepsis and pulmonary haemorrhage, regardless of history of exposure to potential reservoirs such as rats or cattle.

In the presented case, the patient manifested with the clinical of acute dyspnoea, profound hypoxaemia, haemoptysis and diffuse lung infiltration. These are compatible with DAH syndrome. Airway protection and haemodynamic stabilisation are the standard treatment. In case of refractory standard treatment, rescue therapy such as extracorporeal membrane oxygenation should be one the candidate treatment to be considered.

There are some interesting points which need to be addressed. At first, some patients who presented with clinical diagnosis of DAH may not result from systemic vasculitis. Although this is one of the most common causes of DAH, the infectious cause must be considered as well. Early recognition is important because prompt diagnosis and treatment are required for survival.⁷ The clinical clue helping for distinguishing non-infectious cause and infectious cause is clinical presentations, symptoms and signs. This case presented with acute onset of fever and has no suggestive finding of systemic vasculitis, such as history of asthma, sinusitis, history of offending drug use, rash, purpura, arthritis, glomerulonephritis, nor deforming upper airway disease; point out the diagnosis is infectious cause. Recently, we developed a simplified clinical score called Thai-Lepto score, aimed to increase awareness and early recognition of leptospirosis infection. With the cut-off point 5, the Thai-Lepto score showed a sensitivity of 70.6% and a specificity of 76.3%.⁸

However, non-infectious cause cannot be definitely excluded, and the following four conditions should be considered (1) antiglomerular basement membrane antibody disease in limited pulmonary form at the onset, (2) pulmonary-limited microscopic polyangiitis (MPA), (3) ANCA-associated isolated pulmonary capillaritis or (4) idiopathic pulmonary haemosiderosis.⁹ Due to his life-threatening condition, this patient was promptly treated with antibiotics, IVMP and plasmapheresis while waiting the investigation result for identifying the underlying cause. Systemic steroid was discontinued after results of ANCA antibody and anti-GBM antibody showed negative. In part of plasmapheresis, although the mechanism of action has not been fully explained in severe pulmonary haemorrhagic syndrome (SPHS). Suggestion that plasmapheresis has a role in the treatment of severe sepsis caused by leptospirosis, as well as immune complex-mediated organ injury, has been reported.¹⁰ Similar to plasmapheresis, benefit of systemic corticosteroid use in severe leptospirosis was cited in many studies from South Asia, which is an endemic area of leptospirosis.¹¹ However, there is no evidence to suggest that high-dose corticosteroids are effective in severe leptospirosis, and a well-designed randomised clinical trial is needed.¹²

Recently, an increasing number of cases have been reported with pulmonary haemorrhage as a prominent feature, preceding all other manifestation of leptospirosis such as jaundice and acute renal failure.^{2,3} Most of the cases were reported from China, Korea, Nicaragua, Brazil and India.^{1,13-16} In recent studies, stress

that the clinical presentation of this disease has been changed from the more classical syndrome with renal impairment and jaundice has been previously recognised. Leptospirosis with pulmonary involvement has been reported.^{17,18} SPHS or, in another term, severe pulmonary forms of leptospirosis (SPFL) is considered as a form of leptospirosis distinct from Weil's disease because pulmonary presentation has been found to occur independently without renal and hepatic impairment.¹⁹ Manifestations of SPHS, including respiratory distress or pulmonary haemorrhage, are usually massive and potentially leading to ARDS. SPHS has a rapid and severe course with high mortality rates (30%–74%) despite aggressive supportive care.^{3,20} In one series, 74% of 89 fatal cases of leptospirosis had clinically detected pulmonary involvement, which is the strongest predictor of death.²¹ Moreover, the epidemiological setting was changed. Leptospirosis was also found not only in rural areas nowadays, but also increasingly in urban area.²²⁻²⁴

Second, this presented case manifested with only 3 days of fever but it is also a probable leptospiral case. The incubation phase from exposure to onset of symptoms averages from 7 to 12 days, though it can be as short as 3 days or as long as a month.²⁵ On the issue of diagnosis, since clinical and laboratory findings are non-specific, serological test is needed for diagnostic confirmation. In this case, we use molecular diagnosis, real-time PCR assay for a pathogen-specific gene, *lipL32*, which is positive from blood specimen at days 1 and 8 of admission, and negative from urine. This technique's advantage, available in our institute, is short turnaround time; result could be reported within 24 hours. The accuracy of this test was evident in several studies with a sensitivity of 61%–86% and a specificity of 99%–100%. Both high yield and rapidity of the test make it practical in the diagnosis of severe leptospirosis, which needs prompt treatment, and can avoid unnecessary immunosuppressive drugs during management of treatable DAHs.²⁶⁻²⁸ Moreover, we found that *Leptospira* IgM from blood samples was negative in day 1, but turned to positive result later in day 8 (Department of Medical Sciences, Thailand, 2018; sensitivity 92%, specificity 98.7%; compare with microscopic agglutination test). Although no randomised controlled trial comparing PCR and *Leptospira* IgM was reported, our case implies that PCR may be more beneficial especially in the early phase of disease.

Leptospirosis is one of important zoonotic diseases that affect populations particularly in tropical countries. Leptospirosis causes 1.03 million cases worldwide each year and is the cause of 58 900 estimated deaths. Data in Thailand show high morbidity and mortality rates, 39.37 (14.16–77.07) and 2.06 (0.72–0.02) cases per 100 000 population, respectively.²⁹ In table 1, we have summarised the previous case report of severe leptospirosis with pulmonary haemorrhage.³⁰⁻³⁶ Leptospirosis-associated pulmonary haemorrhage syndrome is a severe condition with high mortality.^{3,20,21} Early and intensive management plays a significant role in treatment outcome. Finally, ECMO therapy should be considered early as an adjunctive therapy in patients with severe respiratory failure that is difficult in maintaining adequate oxygenation by conventional mechanical ventilation; because respiratory distress is the most common cause of death in these severe cases of leptospirosis. VV-ECMO was used as adjunct therapy for severe ARDS in leptospirosis.³⁰ Data of ECMO use in the USA increased ninefold, from 165 patients in 2000 to 1450 patients in 2009. This increasing number is occurring in many countries. Even so, the implication of ECMO treatment in low-income countries is a challenging issue. Thailand's health system is composed of primary hospital, general hospital, tertiary hospital and excellence centre. The ECMO

centres are limited. We proposed this case for highlighting the importance of a referral system in low-income countries. This patient is another case of leptospirosis with severe ARDS which was treated with VV-ECMO on the first day of admission.

In conclusion, we successfully treated a patient with leptospirosis-associated SPHS by using VV-ECMO. Our case emphasises that the survival of leptospiral patients with SPHS could be improved by optimal support, including VV-ECMO. A high index of suspicion is required for an early and accurate diagnosis of leptospirosis to guide appropriate treatment, especially in severe respiratory failure.

Patient's perspective

Patient's wife: I appreciatively consent to publish his detailed symptoms. I hope that sharing this case would help other patients who find themselves in similar situations.

Learning points

- ▶ Leptospirosis should be considered by physicians when patients present with fever, sepsis and pulmonary haemorrhage, regardless of history of exposure to potential reservoirs such as rats or cattle.
- ▶ Severe pulmonary haemorrhagic syndrome (SPHS) is considered as a form of leptospirosis distinct from Weil's disease because pulmonary presentation was found to occur independently without renal and hepatic impairments.
- ▶ Real-time PCR assay for pathogen-specific gene, *lipL32*, is a rapid diagnostic tool.
- ▶ Extracorporeal membrane oxygenation therapy should be considered early as an adjunctive therapy in leptospiral patients with SPHS.

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