CASE REPORT

A case of leptospirosis with acute respiratory failure and acute kidney injury treated with simultaneous extracorporeal membrane oxygenation and haemoperfusion

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SUMMARY

A 47-year-old man with a recent history of wading in floodwaters presented with a 1-week history of cough, myalgia, conjunctival suffusion and decreasing urine output. The patient had uraemia, hypotension, leukocytosis, thrombocytopenia, elevated liver enzymes and oliguria. His condition quickly worsened with haemoptysis, and respiratory distress which subsequently required intubation and mechanical ventilation. Continuous renal replacement therapy was started together with haemoperfusion (HP). The patient initially required norepinephrine and this was discontinued after the first session of HP. He was referred for veno-venous extracorporeal membrane oxygenation (ECMO) due to severe hypoxia and pulmonary haemorrhage. Oxygenation and lung compliance improved, and serum creatinine levels continued to normalise with improved urine output. He was placed off ECMO, extubated and eventually discharged. Patient was diagnosed with severe leptospirosis, acute respiratory failure and acute kidney injury successfully treated with simultaneous ECMO and HP. Blood samples were positive for *Leptospira* spp. DNA via PCR assay.

BACKGROUND

The Philippines experiences several typhoons each year resulting in massive floods during the rainy season. In 2009, the very devastating typhoon Ketsana hit the Philippines and caused massive flooding. There was an increase of patients diagnosed with leptospirosis who were admitted to the National Kidney and Transplant Institute (NKTI).

The NKTI is a 350-bed tertiary medical centre for patients with kidney diseases who come from various regional hospitals in the nation. A temporary ward for patients with leptospirosis was set up, in order to accommodate more than 60 patients with leptospirosis during that time. Majority or 83.12% (128 out of 154) of leptospirosis patients developed acute kidney injury (AKI) of which 73.4% necessitated dialysis. Overall mortality was 15.6% and the most common cause was pulmonary haemorrhage.[1] Since then, almost every year, these leptospirosis outbreaks have occured, despite educational campaigns of the government's health department, on antibiotic prophylaxis for this disease. Recently, even without major typhoons, monsoon rains have resulted in similar outbreaks.

Leptospirosis is a bacterial disease caused by exposure of mucous membranes to urine of infected animals, usually rats in urban cities. In its most severe form it results in jaundice, renal failure and pulmonary haemorrhage called Weil's disease. The addition of steroids to standard treatment in various studies resulted from the increasing evidence of an immune-mediated injury underlying the renal failure and pulmonary haemorrhagic complications in leptospirosis via an exaggerated host immune response.[2]

At the NKTI, there was a significant survival benefit (88% vs 74%), and improvement in partial thromboplastin time in patients with severe leptospirosis (prolonged bleeding parameters, AKI and acute lung injury requiring ventilatory support) who were given a 3 day course of intravenous methylprednisolone (MPP) and a single dose of cyclophosphamide (CP), compared with patients given standard therapy plus a 3 day course of hydrocortisone.[3] In our institute, a 3-year review of a protocol using intravenous MPP and CP in 194 patients showed a 25% mortality; 32 (16%) died from pulmonary haemorrhage, 13 (7%) due to multiple organ failure and 4 (2%) due to hospital acquired pneumonia.[2] Significant predictors of mortality included a low platelet count (p value<0.001), prolonged prothrombin time (p value 0.026) and the presence of parenchymal infiltrates on chest radiograph (p value 0.001). Majority of the patients died from pulmonary haemorrhage. All patients who survived, recovered renal function and became dialysis independent after 2 days. Thus, in order to impact survival among patients who develop pulmonary haemorrhage, extracorporeal membrane oxygenation (ECMO) therapy was recommended by the authors.

Recent evidence showed that haemoperfusion (HP) could be used to counter the release of cytokines and other inflammatory markers responsible for cardiovascular instability and collapse requiring the use of inotropic agents for patients who develop sepsis.[4] Hypotension has limited the use of even continuous renal replacement therapy (CRRT) in

Table 1 Summary of laboratory data

Days	0	1	2	3	4	5	6	7	8
Hb (g/L)	12.7	11	10.4	10	10.5	10.6	13	11	11
WBC (x10^9/L)	16.6	16.4	10.6	9.9	11.5	13.7	15	15.1	17
Neutro (%)	71	73	71.2	87	92.7	88.2	89	90.6	89.2
Band (%)	15	6							
Plt (x10^9/L)	63	101	139	122	78	75	67	95	150
PT (s)	12.3		13.3	13	13.1	12.1	12	12.3	12.2
INR	1.17		1.12	1.1	1.1	1.01	1	1.03	1.02
aPTT (s)	66.8		72.8	52	62.4	35.7	41	62.7	62.6
BUN (mg/dL)	85		55	32	64	52	36	54	80
Crea (mg/dL)	6.4		4.4	2.1	3	2.8	2.2	3.2	5
Tbil (mg/dL)		2.3	1.4	1	0.8	1	1.4	1.3	1
GOT (U/L)		364	261	190	117	112	88	45	30
GPT (U/L)	61		64	56	54	62	73	51	37
HS-CRP (mg/dL)		251	125	124	231	793	97		
PCT (ng/mL)		73.8			24.2				
SOFA			16	8	11	11	11	10	8

aPTT, activated partial thromboplastin time; BUN, blood urea nitrogen; Crea, creatinine; GOT, aspartate aminotransferase; GPT, alanine aminotransferase; Hb, haemoglobin; HS-CRP, high-sensitivity C reactive protein; INR, international normalized ratio; PCT, procalcitonin; Plt, platelet count; PT, prothrombin time; Tbil, total bilirubin; WBC, white blood cell.

the treatment of AKI. HP has been shown in limited studies to effectively reduce IL-2, IL-6, TNF alpha and other markers of inflammation, by binding these proteins to sorbents in special cartridges.[5] HP, by removing cytokines, may improve blood pressure, allowing adequate renal replacement therapy.

In this report, we describe a case of severe leptospirosis with acute respiratory failure and AKI successfully treated with simultaneous ECMO and HP.

CASE PRESENTATION

A 47-year-old previously fit and well man with a recent history of wading in floodwaters presented with a 1 week history of cough, colds and myalgia. He eventually sought consult and was found to be hypotensive with elevated serum creatinine levels. He was advised transfer to our institution for renal replacement therapy and was subsequently admitted. During this period, there was an outbreak of leptospirosis patients being admitted into hospital. About 5–10 patients were being admitted each day with severe leptospirosis.

INVESTIGATIONS

Initial examination showed an afebrile patient with a blood pressure of 80/40 mm Hg and pulse of 105 beats/min. Oxygen saturation was 91% at room air. Conjunctival suffusion, slight icterisia, bibasal crackles and bipedal oedema were noted. Serial laboratory investigations demonstrated leukocytosis, thrombocytopenia, elevated serum creatinine, urea, slightly elevated liver enzymes and prolonged bleeding parameters (table 1).

Blood gas analysis showed metabolic acidosis and hypoxaemia with a Pao_2/Fio_2 ratio of 245. Baseline chest X-ray revealed hazy densities in the right mid lung field (figure 1). Blood cultures and endotracheal aspirate culture were done.

DIFFERENTIAL DIAGNOSIS

The patient had a history of wading in floodwaters 1 week prior to admission with a 1-week history of cough, myalgia, conjunctival suffusion and decreasing urine output. The differential diagnoses were pulmonary renal syndromes, dengue or sepsis secondary to pneumonia. However, due to the ongoing leptospirosis outbreak, a high index of suspicion and the clinical features present in this patient made these diagnoses highly unlikely. Pulmonary renal syndromes were ruled out due to its rarity in the Philippines. Dengue may present with AKI and pulmonary haemorrhage, but is very rare. The history of wading in floodwaters favoured the diagnosis of leptospirosis. Sepsis from pneumonia was also considered at that time because of the radiological findings on chest X-ray but could not account for the presence of conjunctival suffusion and myalgia which were experienced by the patient.

Treatment

Initial management included hydration, inotropic support and administration of intravenous ceftriaxone 30 mg/kg once daily. Haemodialysis (HD) was done on day 1 of hospital stay due to oliguria and elevated creatinine. The patient fulfilled our institution's criteria of severe leptospirosis and the protocol for pulse therapy consisting of intravenous MPP 500 mg daily for 3 days

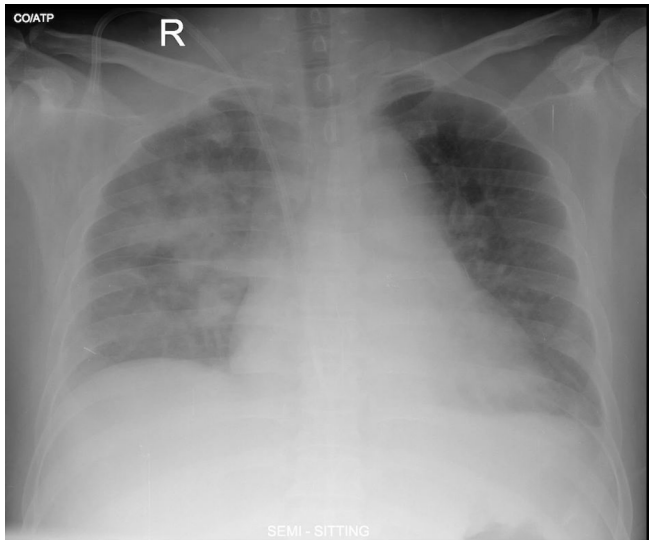

Figure 1 Baseline chest X-ray. Hazy densities are seen in the right mid lung.

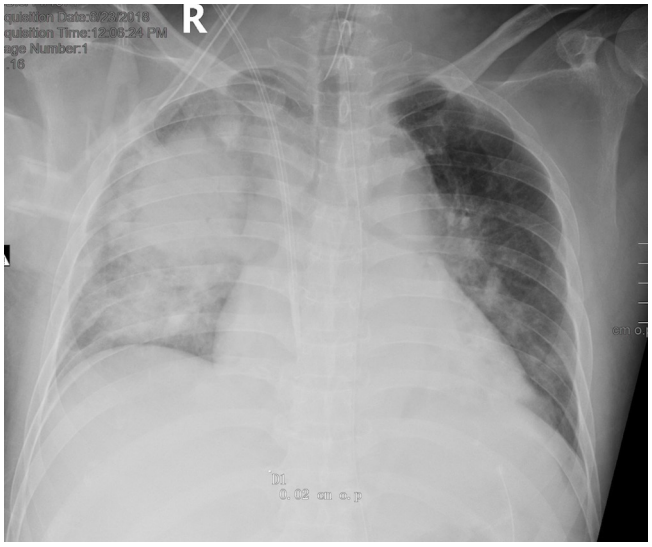

Figure 2 Chest X-ray after intubation. Increase in the hazy densities in the right mid lung, right para cardiac and left para hilar area, which may be due to pulmonary oedema.

commenced. He then had an episode of haemoptysis. Platelet count of 63×10^9/L, prothrombin time of 13.9 s and an activated partial thromboplastin time of 66.8 s were noted (table 1). The patient was given 1 dose of 1 g intravenous CP. Three units of fresh frozen plasma (FFP) were transfused.

Soon after, there was a note of deterioration in sensorium as well as oxygen saturation and he eventually required invasive mechanical ventilation. Arterial blood gas at Fio_2 of 100% showed pH 7.20, PO_2 62, Pco_2 45, HCO_3 17.6, oxygen saturation 85% with Pao_2/Fio_2 of 62. On intubation there was note of bloody aspirate. A second chest X-ray was taken after intubation showing an increase in the hazy densities in the right mid lung, right para cardiac and left para hilar area, which may be due to pulmonary oedema (figure 2). Pulmonary haemorrhage was considered. He was then admitted to the intensive care unit (ICU) with a baseline computed Acute Physiology and Chronic Health Enquiry II score of 20 (35.5% predicted mortality rate). Baseline Sequential Organ Failure Assessment (SOFA) score was 16 with a 90% predicted mortality rate (table 1). In view of the poor oxygenation and the impression of pulmonary haemorrhage, the patient was referred to the pulmonary service for possible ECMO.

The patient was seen by the ECMO team to be agitated and in respiratory distress with oxygen saturation of 80% despite full mechanical ventilatory support. Lung protective strategy using low tidal volume of 300 mL (6 mL/kg), high positive end-expiratory pressure (PEEP) (10–15 cm H_2O) and $Fio_2$100% did not improve oxygen saturation. In addition to this, lung compliance at that time was only 8, and Murray score was 3, hence the decision to initiate veno-venous (V-V) ECMO. Physical examination showed tight air entry with note of bloody secretions per endotracheal tube.

The team decided to initiate V-V ECMO because the patient was severely hypoxic and required high doses of norepinephrine to stabilise his blood pressure. Priming for ECMO was done with 2000 units of unfractionated heparin incorporated in the priming solution. One vial of human albumin 20% and mannitol 2 mL/kg were infused into the patient. Regional anticoagulation with citrate is not available in our institution. Cannulation was performed via femoral catheter F21 for access and femoral catheter F23 for return.

The patient was placed on ECMO Cardiohelp with HLS Set Advanced 7.0 (bioline coating). V-V ECMO was initiated at 2.5 L/min, with sweep gas flow through the oxygenator at 2.5 L/min of 100% oxygen. After the procedure, the patient's SpO_2 was 100%, heart rate was 89 beats/min and blood pressure was 125/95 mm Hg on 0.2 μg/kg/min of norepinephrine.

The ECMO blood flow was maintained at 2.5 L/min during the first 3 days (table 2). Partial thromboplastin time (PTT) was monitored every 6 hours and heparin drip was given to maintain PTT at around 40–60 s.

OUTCOME AND FOLLOW-UP

On the first ECMO day, the mechanical ventilation was set at a tidal volume of 6 mL/kg, PEEP of 5, respiratory rate of 10 per minute and Fio_2 of 40%. The patient was sedated using midazolam and fentanyl drips. Transthoracic echocardiography showed an ejection fraction of 31%; hence, dobutamine was initiated at 2.5 mg/kg/min.

With the patient on dopamine, dobutamine and norepinephrine and severe metabolic acidosis, HP was performed using the HA330 cartridge for 2 hours, and continued for two more consecutive days. The patient was simultaneously started on CRRT that was continued for 4 days. After the first HP, notably norepinephrine was discontinued, followed by dopamine after the second HP and the patient was off all inotropes after the third session. Blood gases showed metabolic acidosis which resolved by the fourth day of CRRT. Baseline high-sensitivity C reactive protein (HsCRP) was elevated at 251 mg/dL and decreased over the next two HP sessions (table 1). However, after the third session, HsCRP again increased to 793 mg/dL; thus, a fourth HP session was done. Urine output started to improve on day 4 of ECMO.

There was a partial clearing of lung infiltrates of chest X-ray on day 5 of ECMO (figure 3). Oxygenation remained stable and lung compliance significantly increased at day 6 of ECMO (table 2). Sweep gas flow was decreased to 2.0 L/min of 100% oxygen and arterial blood gases were monitored (table 2).

Chest X-rays improved, including compliance and oxygenation; thus, a trial without oxygen flow was performed. He was able to tolerate the trial without oxygen flow to the oxygenator overnight (about 12 hours). He was weaned from ECMO on the sixth day; hence, decannulation was done. He was maintained

Table 2 ECMO settings

ECMO day	1	2	3	4	5	6
Flow (L/min)	2.5	2.5	2.5	2.0	2.0	2.0
Gas flow (L/min)	2.5	2.5	2.5	2.0	2.0	2.0
FDO_2	1	1	1	1	1	1
RPM	2110	2045	2020	1800	2000	2000

ECMO, extracorporeal membrane oxygenation; FDO_2, fraction of delivered oxygen; RPM, revolutions per minute.

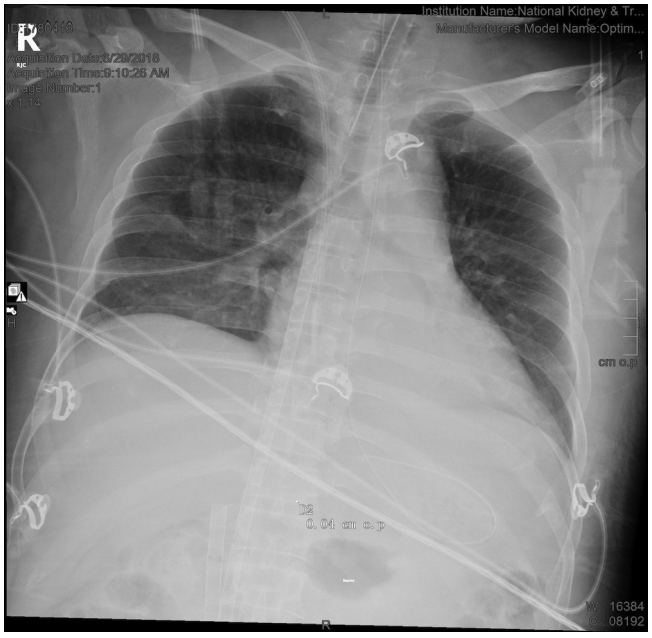

Figure 3 Day 5 extracorporeal membrane oxygenation chest X-ray. There is partial clearing of the hazy densities in the right lung and in the left paracardiac area.

on mechanical ventilation with a tidal volume of 7 mL/kg, PEEP of 5, respiratory rate of 12 per minute and Fio_2 of 40%.

After removal from ECMO, arterial blood gas (ABG) showed a pH of 7.39, Pao2 139 mm Hg, Pco2 38 mm Hg, HCO_3 23 mmol/L,and SaO_2 99%. Chest X-ray after decannulation showed no congestion and no new infiltrates (figure 4). He was extubated 5 days after being taken off ECMO. He was maintained on face mask at 10 L/min and post-extubation ABG showed a pH of 7.40, Pao_2 303 mm Hg, Pco_2 43 mm Hg, HCO_3 26.6 mmol/L and SaO_2 100%; hence, oxygen supplementation was decreased to 6 L/min.

Two days after being taken off ECMO, there was a rise in serum creatinine; thus, he underwent one session of sustained low efficiency dialysis (SLED). Through the subsequent hospital

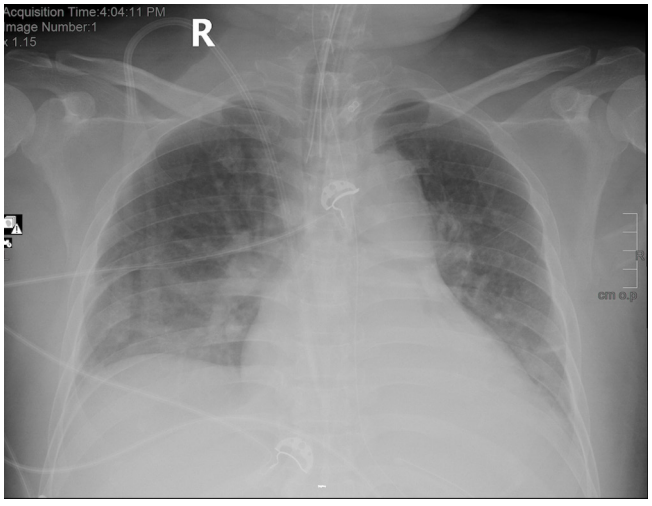

Figure 4 Chest X-ray after extracorporeal membrane oxygenation decannulation. There is almost complete clearing of infiltrates in the right parahilar area. No congestion and no new infiltrates.

course, serum creatinine levels continued to normalise with improved urine output.

The patient stayed in the ICU for 19 days (6 days on ECMO and 12 days on mechanical ventilator). At room air, his oxygen saturation was 98%. Spirometry performed 2 weeks after extubation showed a mild restrictive ventilatory pattern. He tolerated a normal diet and voided freely. Prior to his discharge, last laboratory values were significantly improved. Blood gas showed a pH of 7.46, Pao_2 90 mm Hg, Pco_2 38 mm Hg, HCO_3 27 mmol/L and SaO_2 97%. CBC showed a white blood cell count of 7.32×10^9/L, haemoglobin 110 g/L and platelets 381×10^9/L. Creatinine was at 1.1 mg/dL and total bilirubin was 0.7 mg/dL.

DISCUSSION

Leptospirosis is an endemic zoonosis in the Philippines with an average of 680 leptospirosis cases and 40 deaths from the disease reported every year and a prevalence of 10/100 000.[6] Disasters and extreme weather events are now recognised to precipitate epidemics.[7] Leptospirosis has emerged as an important cause of pulmonary haemorrhage syndrome[8] and AKI due to Weil's disease[9] in many regions where transmission is endemic. Case fatality for pulmonary haemorrhage syndrome and Weil's disease is more than 10% and 70%, respectively.[10]

According to the Philippine's Department of Health (DOH), in 2017 there were 2495 leptospirosis cases, a 49.1% increase from the previous year.[11] The disease predominantly occurs in males (88.8%), mostly between the ages of 15 and 24 years. There were 261 deaths, with the highest case fatality rate of 20% among those aged 45–49 years. As of June 2018, the DOH already recorded a 41% increase in cases nationwide compared with the same period in the previous year, with a 60% increase in leptospirosis in the national capital region. In the NKTI's experience, it is a dreaded disease mainly affecting male family breadwinners, with a mortality rate close to 100% once the patient has pulmonary haemorrhage.

ECMO in leptospirosis

Patients with leptospirosis may present with dyspnea, mild to severe haemoptysis and worst, acute respiratory failure. Pulmonary symptoms usually appear between the fourth and sixth day of disease and the evolution of the disease may become very rapid and may lead to death in less than 72 hours. A severe pulmonary form of leptospirosis has been reported and is seen in less than 5% of patients, characterised by profuse intra-alveolar haemorrhage.[12] This is predominantly a result of capillary involvement and thrombocytopenia.[13] Haemoptysis is reported in 17%–50% of patients[14] and leptospirosis patients who developed acute respiratory distress syndrome (ARDS), requiring mechanical ventilation, had a high mortality rate of up to 51%.[15] It has been suggested that ECMO can improve the outcome[16] of this dreaded complication.

The role of ECMO in ARDS has been controversial, with conflicting data on its effect on survival compared with conventional ventilator management.[17] Nevertheless, four randomised trials have studied the effectiveness of ECMO in respiratory failure.[18] Only a few cases of ARDS due to leptospirosis treated successfully with ECMO have been reported. Umei and Ichiba reported a very similar case in Japan, where a leptospirosis patient with Weil's disease and severe hypoxaemia was referred to their hospital and was successfully treated with V-V ECMO.[19] The patient was cannulated using femoro-jugular approach and stayed on ECMO for 15 days. Similar to our patient with pulmonary haemorrhage, once bleeding was controlled, cautious

anticoagulation with heparin was initiated; they maintained their activated partial thromboplastin time (aPTT) at around 40–50 s.

Pardinas *et al* reported a case of leptospirosis with pulmonary haemorrhage where haemoptysis persisted during V-V ECMO despite an adjusted heparin protocol, necessitating multiple blood transfusions and the use of aminocaproic acid on the 13th day on ECMO.[20] Patient was cannulated using a femoral-femoral approach and was eventually weaned off ECMO after 18 days, with full recovery thereafter. One of the problems frequently encountered in our patient was a frequent chattering of the tubings which resolved after fluid challenges of 100–200 cc normal saline solution. It was very difficult to control the patient's fluids because of this and he gained close to 10 kg during ECMO. Chattering was worse during CRRT and SLED probably because of the additional extracorporeal circuit. Moreover, since we used the femoro-femoral approach, there was some degree of recirculation as evidenced by our high SvO2 of 80%–85%. Nevertheless, oxygen delivery to the patient was deemed sufficient. Chattering and recirculation could probably be avoided using the femoro-jugular approach.

The patient reported by Pardinas *et al* had a normal pulmonary function test at 6 months follow-up despite being on ECMO for 18 days, signifying a complete reversal of his lung injury. Likewise, the NKTI patient was discharged with a mild restrictive ventilatory pattern after 6 days on ECMO and 12 days on mechanical ventilator.

Liao *et al* reported the successful use of V-V ECMO in a leptospirosis patient with pulmonary haemorrhage who developed ARDS with severe hypercapnia.[21] Their patient was on ECMO therapy for 6 days and was transfused a total of 24 units of FFP, 4 units of single donor platelets and 12 units of packed red blood cells. The patient was successfully extubated and was discharged in good condition. The NKTI patient received a total of 6 units of packed red blood cells, 17 units of random platelets, 1 unit of apheresed platelets, 3 units of FFP and 16 units of cryoprecipitate.

Cantwell *et al* also reported the success of V-V ECMO in a leptospirosis-associated catastrophic respiratory failure via femoro-jugular approach.[22] Initially, oxygenation was not adequate; hence, a second membrane oxygenator was added. They emphasised the importance of optimal support, requiring enough membrane surface and flow for an obese, highly hyperdynamic patient. The NKTI patient had adequate oxygenation during ECMO support at 2.0–2.5 L/min blood flow rate.

HP in leptospirosis

AKI is one of the major complications of leptospirosis. The incidence varies from 10% to 60%. Renal involvement in leptospirosis can vary from a subclinical course, with mild proteinuria and urinary sediment abnormalities, to severe AKI.[23] Its presence is a marker of severity and is an indication for hospitalisation as it may portend a poorer prognosis. Renal involvement in leptospirosis varies in severity from mild non-oliguric renal dysfunction to complete renal failure, a hallmark of Weil's syndrome. Acute stages of leptospirosis were characterised by acute tubular necrosis and acute tubulointerstitial nephritis on histopathology.

In patients with Weil's disease, using daily HD to maintain strict control of azotaemia and fluid volume can improve survival, especially for patients who have the potential for pulmonary haemorrhage and are at high risk for death. A study by Andrade *et al* showed that prompt initiation of dialysis, together with daily dialysis sessions, seemed to reduce ICU mortality.[24] In another study by Pasamba *et al* done in NKTI, patients likewise had daily HD until recovery of renal function and all patients were weaned off HD after an average of 2 days regardless of mortality outcome.[2] The NKTI patient underwent early HD on admission due to elevated creatinine levels and oliguria, followed by CRRT for acidosis. Once the patient required pressors for blood pressure maintenance, the patient underwent HP.

The HA type resin cartridge (Lizhu Industries) is an extracorporeal HP device that uses neutral microporous resin, and has been proven to specifically adsorb different mediators such as bilirubin and cytokines. The HA330 resin cartridge has the ability to adsorb various medium-sized factors, including most inflammatory cytokines (IL-1, IL-6, IL-8, TNF alpha), ranging from 6 to 26 kDa. A study by Huang *et al* demonstrated that HA HP elicited significant improvement in outcome and organ dysfunction by the removal of inflammatory cytokines in severe sepsis.[25]

The NKTI patient initially underwent three consecutive sessions of HP together with CRRT to address the sepsis leading to AKI from leptospirosis. There was an improvement in HsCRP levels and SOFA scores, and the patient came off inotropic support after the first HP (table 1). HP allowed adequate renal support through CRRT. There was an increase in HsCRP on day 5 of ECMO; thus, another HP session was done. HsCRP levels eventually decreased to 96.9 mg/dL on day 6 of ECMO and did not increase further. The patient started urinating on day 13 and there was progressive improvement in renal function. It is possible that HP assisted in patient recovery by the control of inflammation as measured by HsCRP and consequently a reduction in inotropic support.

Patient's perspective

I do not remember anything during the time when I was in a deep sleep. I am just grateful that my daughter consented to all the treatments and procedures including extracorporeal membrane oxygenation, haemoperfusions and haemodialysis which give me my second life. I am hoping that my countrymen will take leptospirosis as a serious threat especially during monsoon rain season and will take medication to prevent acquiring leptospirosis as advised by the national government.

Learning points

- This proves that veno-venous extracorporeal membrane oxygenation (ECMO) can be a life-saving therapy in leptospirosis patients with pulmonary haemorrhage and respiratory failure.
- ECMO and haemoperfusion (HP) offer hope to patients with the most severe complications of leptospirosis where mortality is high despite optimum support.
- Combining HP with early hemodialysis can further improve outcomes in patients with severe leptospirosis. To our knowledge, this is the first reported case of a leptospirosis patient successfully managed with HP and ECMO for acute kidney injury and lung haemorrhage.

Contributors JRC was responsible for the preparation of the paper and gave the final approval. RAD was responsible for the acquisition, analysis, or interpretation of data and revised it critically for important intellectual content. MIA cleaned the data and revised the paper. JKGG collected data for the pulmonary part. RS-R collected the initial data and drafted the paper. EC designed data collection tools. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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