Case Report

Successful treatment of severe leptospirosis with steroids and antibiotics: A case report highlighting clinical course and management strategies

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ABSTRACT

Leptospira is the most common zoonotic disease which is now being reported further by physicians due to increased awareness and better testing facilities. Its clinical presentation is varied and most cases resolve spontaneously or even after being mislabeled and treated as viral fever. Those that complicate can cause multiple organ dysfunction syndrome and even fatality. We present the case of a 37-year-old lady with multi-organ dysfunction due to severe icteric leptospirosis and her successful management at our center with antibiotics and steroids. Leptospirosis with its varied presentations is often missed by clinicians not keenly searching for the disease. An ardent eye is a must to clinch the diagnosis and treat early with widely available and effective antibiotics.

Key words: Acute respiratory distress syndrome, Hepatitis, Leptospirosis, Steroids

Leptospirosis is a tropical infectious disease of humans and animals which is caused by spirochetes of the genus *Leptospira*. It is considered the most common zoonosis in the world which is associated with settings of poor sanitation and agricultural occupations involving contact with animals and or contaminated water [1]. Increasingly, adventurous travel and mud sports or races involving freshwater or soil exposure put humans at risk. Affected reservoir species experience chronic colonization of proximal renal tubules and shed leptospires in urine. Humans are accidental hosts and not typically considered reservoirs but may chronically shed leptospires. Diagnosis is guided by a history of exposure and good clinical examination. The patient's presentation usually mimics that of viral fevers. Rarely do cases present with coagulopathy, liver dysfunction, signs and symptoms of meningeal irritation, behavioral change, and breathlessness as multisystem involvement [2]. Therefore, it is important for treating physicians to be aware of the various presentations of leptospirosis and the approach to the management of complicated cases.

This case is to re-emphasize the importance of early diagnosis and prompt lookout for complications in tropical infections. Hereby, we present a case of severe leptospirosis with multiorgan dysfunction with an uncommon presentation.

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CASE REPORT

A 37-year-old female, homemaker with no known comorbidities, was brought to our hospital in a state of altered sensorium by her relatives with a preceding history of continuous fever with chills of 12 days' duration, associated with yellowish discoloration of skin and eyes. There was also a history of insidious and rapidly progressive shortness of breath for 8 days (MMRC I to IV). There was no history of vomiting, cough, melena, hematemesis, or bleeding manifestations.

On arrival, the patient was agitated and was disoriented to time, place, and person. Her temperature was 101°F, her pulse was 70/min (regular), her blood pressure was 146/104 mmHG right arm supine, her respiratory rate was 28/min, and SpO_2 was 88% at room air. She was pale and icteric. Multiple petechiae were noted over both lower limbs, chest, and abdomen. The patient was not following verbal commands and had signs of meningism in the form of neck rigidity with Kernig's and Brudzinski's neck signs being positive. Bilateral pupils were normal in size, position, and reaction. Bilateral plantars were flexor and all reflexes were normal. Respiratory system examination revealed respiratory distress with bilateral basal fine crepitations. Abdominal examination revealed hepatosplenomegaly.

The patient was admitted to the intensive care unit and given immediate oxygen support, intravenous (IV) fluids, third-generation cephalosporins, doxycycline, Vitamin K, and supportive measures.

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Early laboratory investigations (Table 1) revealed anemia, leukocytosis with thrombocytopenia, direct hyperbilirubinemia, and mild transaminitis. Renal function tests were within normal limits. There was a compensated metabolic acidosis with a lactate of 1.7 mmoL/L, coagulopathy with an international normalized ratio (INR) of 2.3, and hyponatremia. Acute phase reactants were raised and bedside chest roentogram was suggestive of acute respiratory distress syndrome (ARDS) (Fig. 1a). Ultrasound (USG) abdomen confirmed hepatomegaly (liver span 19 cm) with raised echotexture, splenomegaly, and dilated portal vein. Electrocardiogram and 2D echocardiography showed normal study and no left ventricular dysfunction. Contrast-enhanced computed tomography chest and abdomen revealed bilateral pleural effusion with bilateral perihilar consolidation and hepatosplenomegaly. Investigations directed toward etiology revealed immunoglobulin (Ig) M positive for *Leptospira*. The rest of the workup including an autoimmune panel suspecting autoimmune hepatitis was negative.

The patient had deterioration in the clinical condition in the form of deep jaundice, increasing oxygen requirement, persistent fever, and worsening sensorium. Cerebrospinal fluid (CSF) studies were done which showed normal cytology and biochemistry. CSF examination with dark field microscopy, Gram stain, and culture reports were also negative. Repeat investigations revealed serially worsening transaminitis and bilirubin levels. Given worsening ARDS (from mildly severe to moderately severe) and acute liver failure, the patient was started on the steroid hydrocortisone 50 mg qid.

The patient began to clinically improve after 12 h of steroids and on day 5 of IV antibiotics, became afebrile with improving sensorium, reduced oxygen requirement, and decreased transaminitis. Repeat chest X-ray on day 7 shows resolving ARDS with decreased oxygen requirement and clearing of lung fields (Fig. 1b). The patient was shifted to the ward on day 8 of admission after 48 h of afebrile period and once she was weaned off oxygen. She was shifted to oral antibiotics and steroids were stopped in 1 week without tapering. She continued to improve and had complete resolution of all symptoms except some jaundice by day 14 of admission post which her antibiotics were stopped and she was discharged to home and kept in follow-up.

The patient was readmitted after 2 weeks with complaints of worsening jaundice with new-onset abdominal distension for 5 days. Her repeat bilirubin was 20 mg/dL with transaminitis and INR was 4.0. USG abdomen revealed mild ascites. The patient underwent liver biopsy under fresh frozen plasma and Vitamin K cover which revealed histomorphology of chronic active hepatitis. She was started on steroids again, oral prednisolone at 30 mg per day, and supportive measures. The patient showed resolution of symptoms with the clearing of jaundice and ascites, improvement of appetite, and normalization of INR. She was gradually tapered off steroids over 30 days and was discharged and followed up after 14 days revealing normal investigations, USG abdomen, and chest X-ray with no evidence suggestive of any residual damage.

DISCUSSION

Leptospirosis is a global zoonotic disease estimated to cause around 1 million cases and 60,000 deaths annually, with the Caribbean, Latin America, the Indian subcontinent, Southeast Asia, Oceania, and to a lesser degree Eastern Europe, represent the primary regions of concern regarding disease [3]. The case positivity rate in the south of India is higher and reported to be around 25.6%, whereas it is 8.3% in the northern part of India and ranges from 3.5% to 3.3% in other parts of the country [4]. Leptospirosis is commonly seen in areas with overcrowding such as in military camps, warships, and refugee containments [5].

A clinical challenge, leptospirosis is a true masquerader, often being misdiagnosed as viral fever with most cases being self-limiting or presenting as undifferentiated fever resolving on their own after being treated with over-the-counter medications. Some, however, do not follow the benign path and due to their rapid multisystem involvement end up being mistreated due to overlapping features with acute viral hepatitis, dengue fever, complicated malaria, scrub typhus, etc., or being prescribed unnecessarily higher antibiotics at various health-care echelons.

Table 1: Initial investigation reports on day 1 of admission

Ser	Investigation	Measurement	Reference range
1.	Hemoglobin	9.1 g/dL	13–18g/dL (males) 12–16g/dL (females)
2.	Total leukocyte count	14300 cells/cmm	4000–11000 cell/cmm
3.	Platelet	70000/mcL	1500000–450000/mcL
4.	Total bilirubin/direct bilirubin	11.4/9.4 mg/dL	0.5–0.9 mgdL-Total bilirubin 0.0–0.4 mg/dL-Direct bilirubin
5.	SGPT/SGOT	155/39 IU/L	10–40 IU/dL
6.	Urea	16 mg/dL	10–45 mg/dL
7.	Creatinine	0.8 mg/dL	0.5–1.4 mg/dL
7.	CRP	Reactive	Qualitative
8.	Serum procalcitonin	1.5 ng/mL	0.10–0.49 ng/mL
9.	D Dimer	1141 ng/mL	<500 ng/mL
10.	Fibrinogen C	274 g/L	2–4 g/L
11.	ANA	Negative	Qualitative

SGPT: Serum glutamic-pyruvic transaminase, SGOT: Serum glutamic-oxaloacetic transaminase, CRP: C-reactive protein, ANA: Antinuclear antibody

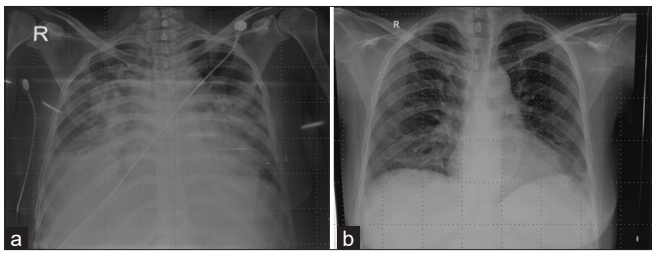

Figure 1: (a) Chest X-ray anterior-posterior (CXR AP) view (supine) shows features of acute respiratory distress syndrome (ARDS); (b) CXR AP view (Supine) on day 7 showing resolution of ARDS

Syndromes caused by leptospirosis are divided into two types, icteric and non-icteric. Icteric leptospirosis affects 5–15% of cases and can lead to rapid multisystem complications causing high mortality of up to 40% [6]. The most common organ to be affected is the kidneys with the onset of acute kidney injury (AKI) presenting as non-oliguric AKI and later progressing to oligo/anuria with proteinuria. Severe leptospirosis has protean manifestations such as diffuse alveolar hemorrhage and ARDS, aseptic meningitis, hepatitis, AKI, hemorrhagic manifestations, and even acalculous cholecystitis and leptospiral pancreatitis have been documented in literature [7]. Moreover, aside from direct microbial injury, the pathogenesis of severe leptospirosis is suggested to involve cytokines generated in response to the infection. It is hypothesized that an excessive immune response may serve as a key contributor to the pathophysiology of leptospirosis. Tumor necrosis factor -alpha, interleukin (IL)-6, IL-10, IL-8, and interferon-gamma have all been incriminated concerning severe leptospirosis [8]. Hepatic necrosis caused by ischemia and destruction of hepatic architecture leads to characteristic jaundice of icteric leptospirosis [9]. The diagnostic criteria of ARDS are reflected in Table 2 [10].

On presentation, our patient came 12 days after symptom onset with jaundice, coagulopathy, hepatitis, ARDS, and encephalopathy. She continued to worsen even on antibiotic support and had to be given steroids which helped regress her symptoms. However, 3 weeks after the short course of steroids, she came back with deepening jaundice, coagulopathy, and ascites with a liver biopsy showing chronic active hepatitis. She had to be reinitiated on high-dose steroids with a gradual taper over a month. This finally led to the resolution of her symptoms and complete clinical recovery.

Diagnosis of leptospirosis remains on clinical suspicion and can be confirmed using Indian council of medical research diagnostic criteria for leptospirosis [11]. Corroboratory investigations may reveal leukocytosis, thrombocytopenia, elevated bilirubin, and a moderate rise in liver enzymes and hyponatremia. Azotemia and proteinuria are also common, however were not seen in our case. Acute phase reactants are typically elevated. A confirmed diagnosis of leptospirosis relies on various criteria such as isolating the organism from the patient, obtaining a positive result through a polymerase chain reaction, detecting seroconversion (microscopic agglutination test), or observing a rise in antibody titer. It is important to note that while IgM tests may show positivity after 72 h, they should not be solely relied upon for confirmation, particularly in the absence of corresponding clinical findings [12].

Table 2: Berlin criteria for the diagnosis of ARDS

Diagnostic criteria of ARDS	
Timing	Within 1 week of a known clinical insult or new or worsening respiratory symptoms
Chest imaging (chest X-ray or CT scan)	Bilateral opacities-not fully explained by effusions, lobar/lung collapse, or nodules
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g., echocardiography) to exclude hydrostatic edema if no risk factor present
Oxygenation	
Mild	200 mmHg PaO_2/FIO_2 ≤300 mmHg with PEEP or CPAP ≥5 cm H_2O.
Moderate	100 mmHg PaO_2/FIO_2 ≤200 mmHg with PEEP ≥5 cm H2O.
Severe	PaO_2/FIO_2 ≤100 mmHg with PEEP ≥5 cm H_2O

CPAP: Continuous positive airway pressure, FIO_2: Fraction of inspired oxygen, PaO_2: Partial pressure of arterial oxygen, PEEP: Positive end-expiratory pressure

Management of leptospirosis is supportive using antipyretics, IV fluids, IV antibiotics, adequate oxygenation, and renal replacement therapy if required. Oral antibiotics doxycycline, amoxycillin, or ampicillin are given for mild leptospirosis, and IV 3rd generation cephalosporins such as ceftriaxone or cefotaxime or doxycycline are given in severe cases. The role of corticosteroids has been reported in many cases and has shown remarkable benefits in severe leptospirosis and those with pulmonary involvement [9]. Despite the mounting evidence, no uniform guidelines regarding steroids in leptospirosis have been proposed. This has led to the usage of high-dose steroids, oral steroids, as well as, methylprednisolone pulse therapy being tried and with reported benefits [13]. However, there is literature warning against the indiscriminate use of steroids in leptospirosis [14]. Plasmapheresis, IV Ig, and even cyclophosphamide have been used in severe leptospirosis, particularly with ARDS and diffuse alveolar hemorrhage, but uniform data are lacking [15].

The available data regarding the use of high-dose corticosteroids in treating leptospirosis derive from five studies discussed under a review study done by Rodrigo *et al.*, each characterized by methodological limitations and small sample sizes. Among these, four studies have reported positive outcomes associated with corticosteroid administration (such as methylprednisolone and prednisolone) in cases of severe leptospirosis featuring pulmonary complications. However, the sole randomized controlled trial, which utilized dexamethasone and prednisolone, did not yield statistically significant benefits. Given the current state of clinical evidence, no definitive recommendation can be made regarding the role of corticosteroids in treating severe leptospirosis. Further randomized controlled trials are imperative to elucidate the potential role of steroids in this context.

Our patient showed clinical response with resolution of encephalopathy and ARDS in response to a short course of steroids and then developed chronic active hepatitis managed on further

high-dose oral steroids with taper over a month. Severe icteric leptospirosis is in itself a rare disease and although literature often reports hepatitis due to *Leptospira*, chronic active hepatitis is a rare presentation. Through this case report, we also wish to reexamine the usage of steroids in severe leptospirosis and urge further guidelines for the same.

CONCLUSION

Leptospira is a disease with varied presentations and can easily be missed by one without a keen eye. Icteric leptospirosis is known to be complicated and can present as multi-organ failure. Early diagnosis and prompt treatment are crucial to limit morbidity and mortality. Diagnosis is clinical and is confirmed using serological and microbiological investigations. Treatment is antibiotics for 7–10 days along with supportive care. Corticosteroids can be given in case of severe leptospirosis. Further studies are needed for uniform guidelines to define the timing and duration of steroids in leptospirosis.

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