CASE IN POINT

Renal Replacement Therapy in a Patient Diagnosed With Pancreatitis Secondary to Severe Leptospirosis

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In areas where the zoonotic disease leptospirosis is endemic, reduced morbidity and mortality is strongly linked to quick initiation of renal replacement therapy.

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Leptospirosis (LS) is considered the most common and widespread zoonotic disease in the world. Numerous outbreaks have occurred in the past 10 years. Due to its technically difficult diagnosis, LS is severely underrecognized, underdiagnosed, and therefore, underreported.[1,2] The Centers for Disease Control and Prevention (CDC) estimate 100 to 150 cases of LS are identified annually in the US, with about 50% of those cases occurring in Puerto Rico (PR).[3] Specifically in PR, about 15 to 100 cases of suspected LS were reported annually between 2000 and 2009, with 59 cases and 1 death reported in 2010. The data are thought to be severely underreported due to a lack of widespread diagnostic testing availability in PR and no formal veterinary and environmental surveillance programs to monitor the incidence of animal cases and actual circulating serovars.[4]

A recent systematic review of 80 studies from 34 countries on morbidity and mortality of LS revealed that the global incidence and mortality is about 1.03 million cases and 58,900 deaths every year. Almost half of the reported deaths were adult males aged 20 to 49 years.[5] Although mild cases of LS are not associated with an elevated mortality, icteric LS with renal failure (Weil disease) carries a mortality rate of 10%.[6] In patients who develop hemorrhagic pneumonitis, mortality may be as high as 50 to 70%.[7] Therefore, it is pivotal that clinicians recognize the disease early, that novel modalities of treatment continue to be developed, and that their impact on patient morbidity and mortality are studied and documented.

CASE PRESENTATION

A 43-year-old man with a medical history of schizophrenia presented to the emergency department at the US Department of Veterans Affairs (VA) Caribbean Healthcare System in San Juan, PR, after experiencing 1 week of intermittent fever, myalgia, and general weakness. Emergency medical services had found him disheveled and in a rodent-infested swamp area several days before admission. Initial vital signs were within normal limits.

On physical examination, the patient was afebrile, without acute distress, but he had diffuse jaundice and mild epigastric tenderness without evidence of peritoneal irritation. His complete blood count was remarkable for leukocytosis with left shifting, adequate hemoglobin levels but with 9×10^3 U/L platelets. The complete metabolic panel demonstrated an aspartate aminotransferase level of 564 U/L, alanine transaminase level of 462 U/L, total bilirubin of 12 mg/dL, which 10.2 mg/dL were direct bilirubin, and an alkaline phosphate of 345 U/L. Lipase levels were measured at 626 U/L. Marked coagulopathy also was present. The toxicology panel, including acetaminophen and salicylate acid levels, did not reveal the presence of any of the tested substances, and chest imaging did not demonstrate any infiltrates.

An abdominal ultrasound was negative for acute cholestatic pathologies, such as cholelithiasis, cholecystitis, or choledocholithiasis. Nonetheless, a noncontrast abdominopelvic computed tomography was remarkable for peripancreatic fat stranding, which raised suspicion for a diagnosis of pancreatitis.

Once the patient was transferred to the intensive care unit, he developed several episodes of hematemesis, leading to hemodynamical instability and severe respiratory distress. Due to anticipated respiratory failure and need for airway securement, endotracheal intubation was performed. Multiple packed red blood cells were transfused, and the patient was started in vasopressor support.

Diagnosis

A presumptive diagnosis of LS was made due to a considerable history of rodent exposure. The patient was started on broad-spectrum parenteral antibiotics, vancomycin 750 mg every 24 hours, metronidazole 500 mg every 8 hours, and ceftriaxone 2 g IV daily for adequate coverage against *Leptospira* spp. Despite 72 hours of antibiotic treatment, the patient's clinical state deteriorated. He required high dosages of norepinephrine (1.5 mcg/kg/min) and vasopressin (0.03 U/min) to maintain adequate organ perfusion. Despite lung protective settings with low tidal volume and a high positive end-expiratory pressure, there was difficulty maintaining adequate oxygenation. Chest imaging was remarkable for bilateral infiltrates concerning for acute respiratory distress syndrome (ARDS).

The coagulopathy and cholestasis continued to worsen, and the renal failure progressed from nonoliguric to anuric. Because of this progression, the patient was started on continuous renal replacement therapy (CRRT) by hemodialysis. Within 24 hours of initiating CRRT, the patient's clinical status improved dramatically. Vasopressor support was weaned, the coagulopathy resolved, and the cholestasis was improving. The patient's respiratory status improved in such a manner that he was extubated by the seventh day after being placed on mechanical ventilation. The urine and blood samples sent for identification of *Leptospira* spp. through polymerase chain reaction (PCR) returned positive by the ninth day of admission. While on CRRT, the patient's renal function eventually returned to baseline, and he was discharged 12 days after admission.

DISCUSSION

The spirochetes of the genus *Leptospira* include both saprophytic and pathogenic species. These pathogenic *Leptospira* spp. have adapted to a grand variety of zoonotic hosts, the most important being rodents. They serve as vectors for the contraction of the disease by humans. Initial infection in rodents by *Leptospira* spp. causes a systemic illness followed by a persistent colonization of renal tubules from which they are excreted in the urine and into the environment. Humans, in turn, are an incidental host unable to induce a carrier state for the transmission of the pathogenic organism.[1] The time from exposure to onset of symptoms, or incubation phase, averages 7 to 12 days but may range from 3 to 30 days.[8]

LS has been described as having 2 discernable but often coexisting phases. The first, an acute febrile bacteremic phase, has been noted to last about 9 days in about 85% of patients, although a minority have persistent fever from 2 weeks to > 30 days. A second phase, the immune or inflammatory phase, is characterized by a second fever spike preceded by 1 to 5 afebrile days in which there is presence of IgM antibodies and resolution of leptospiremia but positive urine cultures.[9] Weil disease may present as the second phase of the disease or as a single, progressive illness from its first manifestation. It is characterized by a triad of jaundice, renal failure, and hemorrhage or coagulopathy.[10] Weil disease is of great concern and importance due to its associated higher mortality than that found with the mildest form of the disease.

There are studies that advocate for RRT as an intricate part of the treatment regimen in LS to remove the inflammatory cytokines produced as a reaction to the spirochete.[11] In tropical countries with a higher incidence of the disease, leptospirosis is an important cause of acute kidney injury (AKI), depending on multiple factors, including the AKI definition that is used.[12] Renal invasion by *Leptospira* spp. produces acute tubular necrosis (ATN) and cell edema during the first week and then could progress to acute interstitial nephritis (AIN) in 2 to 3 weeks. It is believed that the mechanism for the *Leptospira* spp. invasion of the tubules that results in damage is associated with the antigenic components in its outer membrane; the most important outer membrane protein expressed during infection is LipL32. This protein increases the production of proinflammatory proteins, such as inducible nitric oxide synthase, monocyte chemotactic protein-1 (CCL2/MCP-1), T cells, and tumor necrosis factor.[13]

Although doxycycline has been recommended for the prophylaxis and treatment of mild LS, the preferred agent and the conferred benefits of antibiotic treatment overall for the severe form of the disease has been controversial. Traditionally, penicillin G sodium has been recommended as the first-line antibiotic treatment for moderate-to-severe LS.[14] Nonetheless, there has been an increasing pattern of penicillin resistance among *Leptospira* spp. that has prompted the study and use of alternative agents.

An open-label, randomized comparison of parenteral cefotaxime, penicillin G sodium, and doxycycline for the treatment of suspected severe leptospirosis conducted by Suputtamongkol and colleagues showed no difference in mortality, defervescence, or time to resolution of abnormal laboratory findings.[15] Current CDC recommendations include the use of parenteral penicillin 1.5 MU every 6 hours as the drug of choice, with ceftriaxone 1 g administered IV every 24 hours equally as effective.[3]

In addition to antimicrobial therapy, supportive care has shifted to include hemodialysis in those patients who develop AKI as part of the disease. Andrade and colleagues conducted a study of 33 patients with LS in Brazil that was set to compare the impact of door-to-dialysis time and dosage of hemodialysis on mortality. In patients with a quicker door-to-dialysis time and daily hemodialysis sessions, there was a 50% (16.7% vs 66.7%) absolute mortality reduction when compared with those with delayed initiation and alternate-day hemodialysis sessions.[11] A follow-up prospective study compared the use of traditional sustained low-efficiency dialysis (SLED) with the use of extended SLED via hemodiafiltration in patients with LS presenting with ARDS and AKI. Although hemodiafiltration resulted in a relative decrease in serum levels of interleukin (IL)-17, IL-7, and CCL2/MCP-1, there was no significant difference in mortality.[16] The most important prognostic factor in severe LS presenting with AKI and relating to RRT is a shorter door-to-dialysis time and increased dose, not the mode of dialysis clearance. Nonetheless, both RRT methods resulted in a progressive decrease in inflammatory mediators that have been associated with ATN and AIN in the context of LS.[16] The authors argue that using CRRT instead of SLED via hemodiafiltration could have accentuated the effects of the reduction that inflammatory mediators may have on mortality in patients with severe LS.

CONCLUSIONS

LS continues to be of interest due to its current status as the most common zoonotic disease and its widespread prevalence throughout the globe. Novel treatment modalities for LS, specifically for Weil disease, continue to be developed with the goal of reducing the current mortality rate associated with the disease.

In endemic areas, prompt recognition is essential to initiate the recommended therapy. Parenteral antibiotics, such as penicillin G sodium and ceftriaxone, continue to be the mainstay of treatment and constitute the current CDC recommendations. Nonetheless, early initiation of CRRT has been shown to greatly reduce the mortality associated with Weil disease and, when available, should be considered in these patients.

Our patient failed to improve while receiving parenteral antibiotics alone but showed marked improvement after being placed on CRRT. Furthermore, initiation of CRRT resulted in near-complete resolution of his organ dysfunction and eventual discharge from the hospital. This case serves to further support the use of early CRRT as part of the standard of care in severe LS.

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