Increasing awareness of physicians against severe leptospirosis: A treatable but potentially fatal zoonotic infection

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ABSTRACT

Leptospirosis is a worldwide, often severe and potentially fatal zoonotic infection. Here, we present the case of a 35-year-old man with severe leptospirosis infection that was identified early and was treated effectively, with a quite impressive complete recovery. Delaying of early diagnosis and treatment is crucial for the development of an unfavorable clinical course and increases the risk of a lethal outcome.

Keywords: Ceftriaxone, doxycycline, jaundice, leptospirosis, leukocytosis, thrombocytopenia

Introduction

Leptospirosis is a worldwide, often severe, and potentially fatal zoonotic disease, caused by pathogenic serotypes of the spirochete, Leptospira interrogans. Various mammals (especially rodents, cattle, dogs, sheep, goats, and swine) are natural hosts. Rodents are the most important reservoirs for transmission of the disease in most of the cases. Humans are infected incidentally after an animal or environmental exposure, usually from the contaminated environment (e.g., animal urine, contaminated water or soil, infected animal tissue through cuts or abraded skin, mucous membranes, conjunctiva).

Case Report

We present the case of a 35-year-old man that was admitted to our hospital due to intense fatigue, fever, and abdominal pain. His past medical history was free of any chronic diseases, and he reported no substance abuse (including alcohol). The patient, at presentation, was febrile (39°C), had chills, he was well oriented, with no signs of meningismus and reported intense fatigue, progressively worsening over the past 6 days. He also reported fever over the last 4 days that reached 39°C. His arterial blood pressure was 110/80 mmHg; the electrocardiogram showed a sinus rhythm without any abnormal findings, and his pulse was rapid but regular. He reported abdominal pain and during palpation of the abdomen there was an area of mild tenderness over the epigastrium and the right hypochondrium, but with no classic Murphy’s sign and with no hepatomegaly or splenomegaly identified. The rest of the physical examination was unremarkable.

His laboratory work during admission was - white blood cell (WBC): 14.800/µl (neutrophils: 83.4%, lymphocytes: 7.04%), hematocrit (HCT): 39.8%, hemoglobin: 13.2 g/dl, mean corpuscular volume: 91.9 fl, platelet (PLT): 27.500/µl, blood glucose...
level: 106 mg/dl, urea: 37 mg/dl, creatinine: 1.24 mg/dl, serum glutamate oxaloacetate transaminase (SGOT): 109 U/L, serum glutamic pyruvate transaminase (SGPT): 67 U/L, gamma-glutamyl transpeptidase ($\gamma$GT): 198 U/L, alkaline phosphatase: 115 U/L, total bilirubin: 6.5 mg/dl (direct bilirubin: 4.49 mg/dl), International Normalized Ratio (INR): 1.1, K+ : 3.22 mmol/L, Na+: 130 mmol/L, creatinine phosphokinasemia: 1355 U/L, creatine kinase-MB: 33.17 U/L. The rest of the biochemical parameters were normal, urine tests were normal (including serum and urine amylase), chest radiograph was normal and arterial blood gases were also normal. Abdominal ultrasound did not reveal any abnormality. The extensive investigation included a complete screen of viral hepatitis and a screen for Salmonella, Brucella, and Rickettsial infections. Results came out negative.

By excluding other pathologic entities that can present in similar ways, such as pancreatitis, cholecystitis, and based mainly on the clinical and laboratory indicators of the patient and on a high index of suspicion, because the patient was a farmer, handling soil in his everyday activities and living in a rural area that various mammals (especially rodents) exist in high numbers, we suspected Leptospirosis infection at admission to the hospital and we treated him accordingly. Despite the fact that our hospital is one of the largest ones in the area of Central Greece, there was no possibility at that time to perform serology tests for the identification and confirmation of our clinical diagnosis. Rattus norvegicus (also referred to as common rat or brown rat) has been identified in the past as the dominant rat in the area (island of Evia, Greece). This rodent has spread to all continents of the world except Antarctica and is the dominant rat in Europe and much of North America.\[5,4\]

The patient received treatment with oral doxycycline 100 mg twice daily. On the 2nd day from admission, his clinical condition was the same, but his laboratory tests were worsening as follows: WBC - 18.100/µl (neutrophils - 76%, lymphocytes - 9.57%), HCT - 35.1%, PLT - 42.9/µl, urea - 50 mg/dl, creatinine - 1.59 mg/dl, SGOT - 130 U/L, SGPT - 68 U/L, $\gamma$GT - 139 U/L, total bilirubin - 11.41 mg/dl (direct bilirubin - 8.17 mg/dl), albumin - 2.49 g/dl, INR - 1.46, C-reactive protein - 169.73 mg/L.

Due to high concern, based on the clinical condition of the patient along with the impaired hematology profile (leukocytosis, thrombocytopenia) and impaired renal and liver function with worsening jaundice, we decided to add ceftriaxone 2 g daily to the treatment regimen. Ceftriaxone is a well-known drug used for the treatment of leptospirosis, but to our knowledge, there is no reported case in the literature, of ceftriaxone used in combination with doxycycline for the treatment of severe leptospirosis infection.

On the 3rd day from admission, the patient presented with a quite impressive recovery of his clinical symptoms and on the 4th day he had a complete recovery of his general well-being. He reported no fatigue, no abdominal pain, and was afebrile. His laboratory work was still abnormal though, as follows: WBC - 22.800/µl (neutrophils - 57%, lymphocytes - 18%), HCT - 31.9%, PLT - 110.000/µl, urea - 33 mg/dl, creatinine - 1.1 mg/dl, SGOT - 167 U/L, SGPT - 181 U/L, $\gamma$GT - 226 U/L, total bilirubin - 4.02 mg/dl (direct bilirubin - 2.68 mg/dl), albumin - 3.1 g/dl, INR - 1.2.

Serology was eventually performed to a larger diagnostic facility and confirmed the diagnosis of Leptospira interrogans infection. The results of serology (after 8 days of treatment) were the following: anti-Leptospira IgM – <10 and anti-Leptospira IgG - <17. The patient received treatment for a total of 10 days. At the end of treatment, the physical examination was unremarkable, and the laboratory tests were all completely normal.

**Discussion**

This is a case of severe leptospirosis infection with liver and kidney impairment, severe jaundice, thrombocytopenia, and increased WBC counts in an otherwise completely healthy, young individual. The patient's life was eventually saved, due to early recognition of the severity of disease, based mainly on appropriate indicators of severity of disease and appropriate medical treatment. The severe form of the disease (Weil syndrome) is mainly characterized by liver damage with jaundice, impaired kidney function, and finally multi-organ failure, followed by death. In severe cases of leptospirosis, there is a high mortality rate reaching 5%–40%.\[5,4\]

Identification of early indicators of severe disease may result in improved outcome. Reduced PLT counts, increased serum creatinine, increased WBC counts, dyspnea, hemoptysis, and jaundice are important identified indicators that have been associated with severe or fatal outcomes in leptospirosis patients. One more identified important risk factor for the development of severe leptospirosis is a delay of 2 days following the start of symptoms in the initiation of antibiotics.\[6-10\] The patient in our case developed severe leptospirosis infection, which was identified early, based on the indicators mentioned above, and was treated appropriately, with a quite impressive complete recovery. A significant observation was the immediate recovery of the PLT counts (apart from the clinical and general well-being of the patient) after the initiation of treatment with ceftriaxone, which was added to the already administered treatment with doxycycline. We consider this as a possible new significant laboratory indicator of improved outcome after severe leptospirosis infection. Larger confirmatory studies could provide more details on this significant observation.

Till now, there is no reported case in the literature of ceftriaxone used in combination with doxycycline for treatment of severe leptospirosis. Early recognition of potentially severe cases, as well as recognition of indicators of severe disease, will guide primary and hospital care physicians accordingly in taking early appropriate action toward the prevention of full-blown disease and decreasing severe complications and mortality.
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Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References
1. Hartskeerl RA, Collares-Pereira M, Ellis WA. Emergence, control and re-emerging leptospirosis: Dynamics of infection in the changing world. Clin Microbiol Infect 2011;17:494-501.
2. Guerra MA. Leptospirosis: Public health perspectives. Biologicals 2013;41:295-7.
3. Sharp TM, Rivera García B, Pérez-Padilla J, Galloway RL, Guerra M, Ryff KR, et al. Early indicators of fatal leptospirosis during the 2010 epidemic in Puerto Rico. PLoS Negl Trop Dis 2016;10:e0004482.
4. Dupont H, Dupont-Perdrizet D, Perie JL, Zehner-Hansen S, Jarrige B, Dajardin JB. Leptospirosis: Prognostic factors associated with mortality. Clin Infect Dis 1997;25:720-4.
5. Chaniotis B, Psarulaki A, Chaliotis G, Gozalo Garcia G, Gozadinos T, Tselentis Y. Transmission cycle of murine typhus in Greece. Ann Trop Med Parasitol 1994;88:645-7.
6. Haake DA, Levett PN. Leptospirosis in humans. Curr Top Microbiol Immunol 2015;387:65-97.
7. Goswami RP, Goswami RP, Basu A, Tripathi SK, Chakrabarti S, Chattopadhyay I. Predictors of mortality in leptospirosis: An observational study from two hospitals in Kolkata, Eastern India. Trans R Soc Trop Med Hyg 2014;108:791-6.
8. Tubiana S, Mikulski M, Becam J, Lacassin F, Lefèvre P, Gourinat AC, et al. Risk factors and predictors of severe leptospirosis in New Caledonia. PLoS Negl Trop Dis 2013;7:e1991.
9. Spichler AS, Vilaça PJ, Athanazio DA, Albuquerque JO, Buzzar M, Castro B, et al. Predictors of lethality in severe leptospirosis in urban Brazil. Am J Trop Med Hyg 2008;79:911-4.
10. Hochedez P, Theodose R, Olive C, Bourhy P, Hurtrel G, Vignier N, et al. Factors associated with severe leptospirosis, Martinique, 2010-2013. Emerg Infect Dis 2015;21:2221-4.