KI REPORTS
KIReports.org
NEPHROLOGY ROUNDS

Atypical Renal Presentation in Severe Leptospirosis

Michał Małecki[1], Edyta Gołembiewska[1], Anna Maria Muraszko[1], Beata Fiecek[2], Magda Lewandowska[3], Elżbieta Urasińska[3], Joanna Stępniewska[1], Maciej Fijałkowski[1] and Kazimierz Ciechanowski[1]

[1]Department of Nephrology, Transplantology and Internal Medicine, Pomeranian Medical University, Szczecin, Poland; [2]Laboratory of Rickettsiae, Chlamydiae and Spirochetes, National Institute of Public Health, Warsaw, Poland; and [3]Department of Pathology, Pomeranian Medical University, Szczecin, Poland

Correspondence: Michał Małecki, Department of Nephrology, Transplantology and Internal Medicine, Pomeranian Medical University, al. Powstańców Wielkopolskich 72; 70-111 Szczecin, Poland. E-mail: michalmalecki85@gmail.com

Kidney Int Rep (2019) **4,** 168–170; https://doi.org/10.1016/j.ekir.2018.08.007

INTRODUCTION

Weil disease is a rare autoimmune complication of leptospirosis. It develops following a phase of bacteremia, after the pathogens have been eliminated from the bloodstream, but antibody-mediated processes continue to affect the patient's internal organs. In most cases, symptoms appear around 3 weeks after exposure, presenting as acute kidney injury and high-grade hyperbilirubinemia.

CASE PRESENTATION

A 72-year old Caucasian man with no prior medical history was admitted with acute renal failure and hyperbilirubinemia. Three weeks prior to hospitalization, he experienced an episode of fever, accompanied by chills. The initial symptoms were followed by muscle pain and decreased exercise tolerance. Visible jaundice and steadily decreasing urinary output appeared soon thereafter. Three days later he was admitted to a provincial hospital.

Initial tests revealed high total bilirubin levels in the serum, exceeding 20 mg/dl, predominantly conjugated, increased serum inflammatory factors (C-reactive protein levels >90 mg/l), and an elevation of both creatinine and urea serum levels (8 mg/dl and 300 mg/dl, respectively). Serum concentrations of other markers of hepatic damage, such as alanine- and glutamate-pyruvate transaminase, prothrombin time, and alkaline phosphatase, were all within normal ranges. A decrease in both total serum protein (44 g/l) and albumin (24 g/l) was noted. Urinalysis revealed erythrocyturia and proteinuria exceeding the nephrotic-range threshold. Full blood count analysis showed a decreased platelet count (30,000/ml) and mild anemia (Hgb level 9.2 g/dl). A chest X-ray and abdominal computed tomography scan were normal. Serological tests for hepatitis B virus and hepatitis C virus infection were negative.

Initial treatment involved continuous renal replacement therapy and empirical antibiotic therapy with cephalosporin (cefotaxime).

The patient was transferred to our hospital for further investigation and treatment. At the time of transfer, the patient exhibited cognitive impairment, disorientation, hiccups, and Cheyne–Stokes breathing. Physical examination revealed normal vital signs, jaundice, bilateral conjunctivitis, generalized edema, and signs of thrombocytopenic purpura. There were no signs of circulatory or respiratory failure, and no focal neurological signs. Urinalysis showed severe proteinuria (urinary protein 475 mg/dl) accompanied by erythrocyturia (erythrocytes were covering the whole field of vision, and the number of leukocytes were 2 and 5 in the field of vision). The creatinine level was 7.5 mg/dl. The serum level of creatinine phosphokinase (CPK) was CK = 31 U/l (normal), and the serum level of potassium was 5.0 mmol/l.

As jaundice and oliguria requiring renal replacement therapy persisted and a review of the patient's history revealed that he lived close to a river bank and a lake, the suspicion of a Leptospira infection was raised. Blood and urine samples were collected for polymerase chain reaction evaluation of Leptospira pathogen presence and a microscopic agglutination test. In the presence of the severe encephalopathy observed, the decision was made to perform albumin plasmapheresis. After 2 sessions, the mental status of the patient markedly improved. After that point, the patient continued only treatment with hemodialysis, and his

Table 1. Kidney biopsy results

Bioptate 12 mm long (preserved in paraffin block), containing mostly renal cortex
Glomeruli (n = 27)
• 1 glomerulus sclerotic
• 26 glomeruli without pathological findings
Interstitial tissue
• Lymphoid cells, plasmocytes, and single neutrophil; infiltration of up to 10% of bioptate surface
• Edema
Tubules
• Atrophy of 2 tubules
• Some tubules presenting signs of ATN
• Some tubules containing erythrocyte rolls
Vessels
• Arteries: small-grade fibrosis of internal membrane
• Arterioles: unchanged
• Inflammatory cells present in peritubular capillaries
Immunohistochemistry
Glomerular deposits
• IgA (–), IgG (–), IgM (+ in mesangium)
• C1 (+ in mesangium), C3 (–), C9 (–)
Conclusion: Histopathological image together with clinical data suggest changes secondary to leptospirosis.

ATN, acute tubular necrosis.

urine output started to increase significantly. Subsequently, Leptospira tests showed the microscopic agglutination test results as highly positive with an antibody titer of 1:3600, but the polymerase chain reaction test was negative in both urine and blood.

The patient's physical condition continued to improve, with most of the signs present on admission subsiding completely. In view of persistent renal dysfunction, kidney biopsy was performed (Table 1). Using Grocott's methenamine silver staining protocol, cellular inclusions resembling intact Leptospira were found in the tubular lumen of the kidney biopsy specimen (Figure 1).

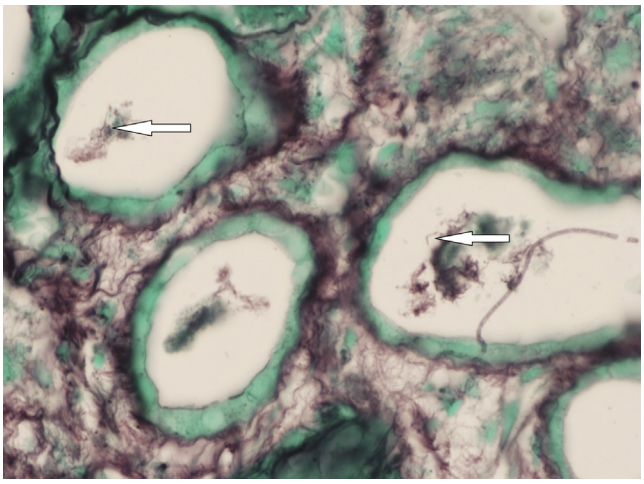

Figure 1. Kidney biopsy specimen. Grocott's methenamine silver staining revealing inclusions (arrows) resembling *Leptospira* in the lumen of renal tubules (original magnification ×100).

Following the biopsy, a 3-day course of i.v. methylprednisolone infusions (250 mg/d) was prescribed, followed by a conversion to oral prednisone (20 mg per day). This resulted in a marked increase in the patient's urinary output, which rose up to 6000 ml per day, accompanied by a continuous drop in serum creatinine and bilirubin levels (Figure 2). Within 1 week, the dialysis treatment was suspended, and bilirubin and hematological parameters returned to normal levels. Three more weeks of continued prednisone therapy resulted in a serum creatinine level of 1.3 mg/dl, with no proteinuria or other abnormal findings on urinalysis. The serum bilirubin and inflammatory marker concentrations all returned to normal. At the time of discharge, the patient was on 20 mg of prednisone, with a planned weekly dose reduction of 5 mg. During a clinic visit 4 weeks later, the patient was asymptomatic, with normal physical examination findings.

DISCUSSION

Weil disease is the most severe presentation of leptospirosis, with a reported mortality rate often exceeding 22%.[1] In most cases, kidney involvement in Weil disease presents as acute renal failure involving oliguria, hypokalemia, loss of urinary concentration ability, albuminuria and hematuria.[1,2] Most commonly, the renal involvement occurs as a result of interstitial damage (inflammation or necrosis), with the glomeruli remaining unaffected. On admission, our patient suffered from nephrotic-range proteinuria accompanied by anasarca, with the kidney biopsy specimen revealing typical interstitial inflammation without any glomerular involvement on light microscopy. In the course of the treatment, urinalysis results returned to normal. Electron microscopic evaluation of the biopsy specimen was not performed; however, podocytopathy (e.g., minimal change disease) is a highly possible explanation of nephrotic-range proteinuria in this case.

The treatment of Weil disease is not standardized. Typically, improvement in kidney function usually can be achieved within several days of antimicrobial and dialysis treatment.[3,4] However, in our case, the time interval between the onset of initial symptoms (fever, fatigue, myalgia) and the hospital admission exceeded 3 weeks, with persistence of symptoms despite antibiotics. Following corticosteroids, continued antibiotics, plasmapheresis, and a hemodialysis regimen, the patient's general condition began to improve. His mental status improved significantly after 2 plasmapheresis sessions. It is hypothesized that antibody-mediated damage to the nervous system could lead to encephalopathy, and prompt neurological recovery following

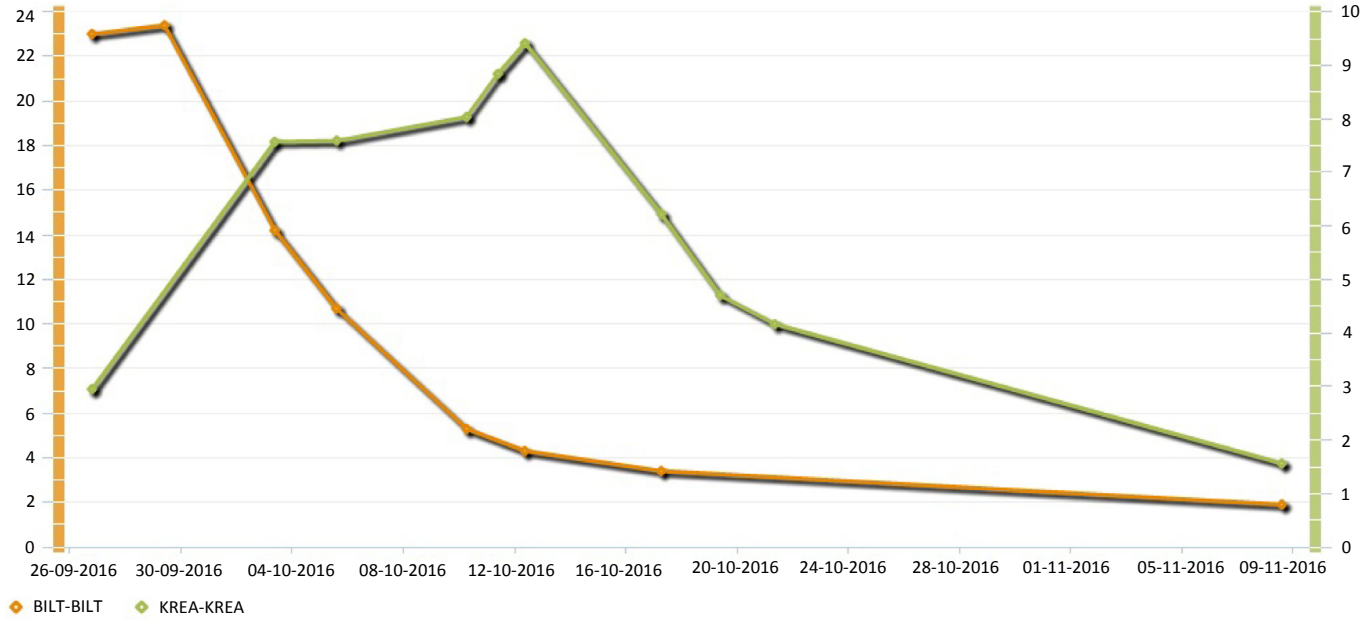

Figure 2. Graph showing serum creatinine and total bilirubin levels during treatment. Treatment regimen: Biotaksime 2 × 1 g i.v. 28.09 to 21.10.2016; methylprednisolone (250 mg) i.v. 14 to 16.10.2016; Encortone 20 mg orally 17.10.2016; hemodialysis sessions (8 in total) 28.08, 30.09, 02.10, 04.10, 08.10, 12.10, 14.10, and 17.10.2016; plasmapheresis sessions (2 in total) 27.09 and 29.09.2016.

plasmapheresis[5] with no recovery of the kidney function.

I.v. methylprednisolone infusions, on the other hand, led to polyuria and a decrease in serum creatinine level. The improvement in kidney function was parallel to jaundice resolution.

Leptospira tests showed polymerase chain reaction—negative results and positive microscopic agglutination test results confirming *Leptospirosis* infection.[6] Because Leptospira are present in the bloodstream for about 7 to 14 days following infection, with urinary presence lasting for about 1 month, no bacterial DNA was found in either of the samples collected for polymerase chain reaction testing, suggesting that the persistent symptoms were from the immune response to infection.[7]

Table 2. Teaching points

1. Kidney injury in leptospirosis can present as nephritic-range proteinuria
2. Combined treatment with plasmapheresis, dialysis, and glucocorticosteroid therapy seems a proper treatment option for a severe course of leptospirosis complicated by kidney injury
3. A microscopic agglutination test is the best diagnostic tool for confirming infection with leptospira
4. Weil disease is a life-threatening condition with a mortality rate exceeding 20%
5. In most cases, kidney damage is limited to the interstitial tissue; glomeruli remain intact
6. Antibiotic therapy with cephalosporins or β-lactam antibiotics should be started in every case of confirmed leptospirosis; in most cases, patients treated with antibiotic with early-diagnosed Weil disease do not need kidney replacement therapy

CONCLUSION

In severe persistent Weil disease, treatment with combined therapy involving antibiotics, plasmapheresis, hemodialysis, and glucocorticosteroid therapy may be required to accelerate recovery (Table 2).[4]

DISCLOSURE

All the authors declared no competing interests.

REFERENCES

1. Daher Ede F, de Abreu KL, da Silva Junior GB. Leptospirosis-associated acute kidney injury. *J Bras Nefrol*. 2010;32:400–407.
2. Gancheva G. Renal involvement in leptospirosis. *J IMAB*. 2012;18:3.
3. Silva F, Brandão M, Esteves A. A rare presentation of leptospirosis. *EJCRIM*. 2016;3:https://doi.org/10.12890/2016_000447.
4. Trivedi SV, Vasava AH, Bhatia LC, et al. Plasma exchange with immunosuppression in pulmonary alveolar haemorrhage due to leptospirosis. *Indian J Med Res*. 2010;131:429–433.
5. Lepur D, Himbele J, Klinar I, et al. Anti-ganglioside antibodies-mediated leptospiral meningomyeloencephalopolyneuritis. *Scand J Infect Dis*. 2007;39:5.
6. Chirathaworn C, Inwattana R, Poovorawan Y, Suwancharoe D. Interpretation of microscopic agglutination test for leptospirosis diagnosis and seroprevalence. *Asian Pac J Trop Biomed*. 2014;4(suppl 1):162–164.
7. Denipitiya DT, Chandrasekharan NV, Abeyewickreme W, et al. Application of a real time polymerase chain reaction (PCR) assay for the early diagnosis of human leptospirosis in Sri Lanka. *Biologicals*. 2016;44:497–502.