Acute Renal Failure Due to Leptospirosis in a Renal Transplant Recipient: A Brief Review of the Literature

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ABSTRACT
We present the case of a 43-year-old renal transplant patient who presented with fever, malaise, pruritus, headache, and severe jaundice of 3-week duration following work in a rice field. He was found to have acute renal failure and severe hyperbilirubinemia with a positive serum leptospira antibody titer, making the diagnosis of Weil’s disease. The patient responded to reduction in immunosuppressive medications and intravenous penicillin therapy with no need for dialysis. This is the second case of leptospirosis in a kidney transplant patient reported in the English literature.

LEPTOSPIROSIS is a zoonotic disease caused by the spirochete Leptospira interrogans with a worldwide distribution, but more commonly in the tropics. The disease is quite prevalent in the northern provinces of Iran, especially among rice field workers. There are 30 serogroups of leptospires and approximately 240 serotypes. The alkaline urine in rodents favors its growth. The rodents, especially rats, are an important reservoir. Other mammals, such as cattle, pigs, hamsters, dogs, jackals, foxes, marsupials, and raccoons, also serve as hosts to the bacteria. The disease is transmitted from animals to humans via infected urine or via an environment that is contaminated with the microorganism. The bacterium enters the host through abraded skin or mucosa and then spreads throughout the bloodstream to various organs. The animal reservoirs carry the microorganism for a long time in their proximal tubules and shed them in their urine. Leptospires establish a symbiotic relationship with their hosts and can persist in their renal tubules for years. The disease can be subclinical; however, a recent study showed that clinical manifestations (i.e., fever, myalgia, headache, conjunctival suffusion, renal failure, jaundice, and hypotension) may be observed in over 60% of patients. Multiple organ damage occurred in 22% of patients. Weil’s disease represents leptospirosis with renal failure and jaundice. Leptospirosis occurs sporadically throughout the year with the peak incidence during the summer months. In a report from Israel, the disease was associated with jaundice in 71%, acute renal failure (ARF) in 62%, rhabdomyolysis in 52%, pancytopenia in 28%, respiratory failure in 14%, and disseminated intravascular coagulation in 5% of the cases.

Herein we have reported a case of a young man who, 2 years after successful kidney transplantation, contracted Weil’s disease after working in a rice field. His renal failure responded to a reduction in immunosuppressive drugs, as well as intravenous penicillin administration. The patient’s renal function returned to baseline 1 month after diagnosis and institution of appropriate therapy.

CASE REPORT
A 43-year-old Iranian man who had received a living unrelated renal transplant in 1998 was admitted in the summer of 2000 because of fever, jaundice, anorexia, malaise, and pruritus, and headache of 3-week duration. Fever vanished for a short period of time and then reappeared. The patient’s past medical history was only significant for posttransplantation type II diabetes mellitus. The patient was a farmer who walked barefoot in water-filled rice fields. The patient was on a regimen of neoral (cyclosporine, Novartis Pharmaceutical) 100 mg twice a day, azathioprine 100 mg once a day, and prednisone 10 mg once a day. On physical examination, his weight was 62 kg, blood pressure was 130/80 mm Hg, no orthostatic hypotension was detected. Jugular venous pressure was normal, temperature was 37.8°C, respiratory rate was 20/min, and pulse rate was 90/min. The patient was icteric with bilateral conjunctival suffusion. The rest of the examination was within normal limits with no peripheral lymphadenopathy, organomegaly, or tenderness upon abdominal examination, and also no muscle tenderness. The patient’s urinary output was adequate.

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Transplantation Proceedings, 39, 1263–1266 (2007) 1263
Laboratory Data

Two months prior to this admission, his routine laboratory studies were as follows: blood urea nitrogen (BUN) 22 mg/dL, serum creatinine 1.3 mg/dL, and normal liver enzymes. His laboratory data on the day of admission and during the following 6 months are shown in Table 1. The liver enzymes were more than four times the upper limit of normal with significant hyperbilirubinemia. Creatinine kinase level was normal. His serum creatinine was 3.9 mg/dL, BUN of 40 mg/dL, Na 132 mEq/L, total serum cholesterol 200 mg/dL, triglycerides 220 mg/dL, and normal thyroid function tests. His urinalysis revealed uric acid 6.0 mg/dL, total serum cholesterol 200 mg/dL, triglycerides mg/dL, Na 132 mEq/L, potassium 3.9 mEq/L, blood sugar 235 mg/dL, with a creatinine clearance of 29 mL/min. The cytomegalovirus antibody titers were positive for immunoglobulin (Ig) G at 92 units/10^6 and negative for IgM. Herpes simple virus antibody titers (IgG, IgM) were negative. Epstern Barr virus antibody screen was positive for IgG and negative for IgM. Whole blood cyclosporine concentration 1 week after admission was 404 ng/mL. Hepatitis B surface antigen, hepatitis B core antibody, and hepatitis C antibody titers were all negative. Serum leptosira antibody titers measured by immunofluorescent technique was positive at 1:400 (normal value < 1:100) on the sixth day of admission. An abdominal ultrasound examination was within normal limits.

Hospital Course

With the impression of leptospirosis, azathioprine was discontinued for the subsequent 4 weeks, and prednisone was initially increased to the maintenance dose. To reduce the immunosuppression, cyclosporine dose was decreased, and the patient was treated with intravenous penicillin G at 2 × 10^6 units every 4 hours for a period of 10 days. The patient did not require any dialysis therapy and was discharged from the hospital after 10 days in good general condition. His renal function returned to normal within 1 month of follow-up; however, it took several months for his liver enzymes and serum bilirubin to return to normal (Table 1).

DISCUSSION

In the only previous report of ARF due to leptospirosis in a renal transplant patient from Brazil, the patient was speculated to have contracted the disease through the wounds on his hands after contact with rat tissues 10 days prior to the onset of his illness. The patient developed severe ARF requiring temporary peritoneal dialysis, and he responded to a reduction in immunosuppressive regimen and intravenous penicillin, with a total recovery of renal function.

In a review of 50 cases reported from Portugal, 90% of the patients lived in rural regions, 64% were at occupational risk for the infection, and 70% had contracted the disease during the summer period. Weil’s disease (ARF and severe jaundice) was diagnosed in 62% of the patients, 35% of whom required hemodialysis with a 6% mortality rate. In a prospective cohort of 121 patients from Thailand, three fourths of the patients were farmers. The cause of death included different combinations of pulmonary hemorrhage, ARF, respiratory failure, acute respiratory distress syndrome, and irreversible shock. The authors found four independent risk factors associated with mortality: hypotension, oliguria, hyperkalemia, and pulmonary rales.

Renal involvement is common in leptospirosis and may be manifested as abnormal urine sediment to severe renal failure. Tubulopathy and hypokalemia occur frequently. ARF has been observed in 44% to 67% of the patients. Interstitial nephritis is the basic renal pathology and together with acute tubular necrosis is responsible for the vast majority of cases. Hemodynamic alterations and hypotension also contribute significantly to the development of ARF in a majority of the patients. Bacterial invasion and toxicity of the bacterial products, especially the outer membrane proteins, with generation of inflammatory cytokines, chemokines, and cellular infiltrate are important in inducing renal injury. The pathogenic leptospires have been shown to invade the proximal tubular epithelial cells. Bacterial lipopolysacharides and outer membrane proteins are transported from the tubular lumen to the interstitium either by active transport or through the damaged tubular epithelium. Moreover, they activate complement, causing

Table 1. Laboratory Data Before and After Development of Leptospirosis

<table>
<thead>
<tr>
<th></th>
<th>04/19/2000 Before Leptospirosis</th>
<th>06/20/00</th>
<th>06/22/00</th>
<th>07/02/00</th>
<th>07/09/00</th>
<th>07/23/00</th>
<th>08/02/00</th>
<th>12/11/00</th>
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<tbody>
<tr>
<td>BUN (mg/dL)</td>
<td>22</td>
<td>40</td>
<td>28</td>
<td>33</td>
<td>34</td>
<td>63</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Cr (mg/dL)</td>
<td>1.3</td>
<td>3.9</td>
<td>2.3</td>
<td>2.8</td>
<td>3.4</td>
<td>1.3</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>AST (IU/L)*</td>
<td>150</td>
<td>120</td>
<td>72</td>
<td>86</td>
<td>160</td>
<td>51</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>ALT (IU/L)*</td>
<td>186</td>
<td>141</td>
<td>110</td>
<td>105</td>
<td>254</td>
<td>85</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Bilirubin Total</td>
<td>—</td>
<td>17.9</td>
<td>19.6</td>
<td>23</td>
<td>23</td>
<td>20</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>Bilirubin Direct</td>
<td>—</td>
<td>10.8</td>
<td>12.5</td>
<td>16.4</td>
<td>18</td>
<td>14</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>120</td>
<td>102</td>
<td>151</td>
<td>115</td>
<td>—</td>
<td>—</td>
<td>126</td>
<td></td>
</tr>
<tr>
<td>LDH (IU/L)‡</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>380</td>
<td>—</td>
<td>—</td>
<td>489</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Cr, creatinine; LDH, lactate dehydrogenase.

*Normal value < 40 IU/L.
†Normal value < 140 IU/L.
‡Normal value < 500 IU/L.
cellular damage and interstitial inflammation. Glycoproteins of leptospires, expressed in renal tubules and vascular endothelial cells, act as potent inhibitors of Na\(^+-\)K\(^+\) adenosine triphosphatase activity of renal tubular epithelial cells.\(^8\) Moreover, the outer membrane proteins induce expression of inducible nitric oxide synthetase, monocyte chemoattractant protein 1, and tumor necrosis factor by the medullary thick ascending limb.\(^9\) Nitric oxide released by the medullary thick ascending limb generates peroxynitrite, which would cause renal injury.

While penicillin remains the drug of choice in the treatment of leptospirosis, other antibacterial agents, such as streptomycin, erythromycin, tetracycline, doxycycline, and cephalosporins, are also effective. In patients with severe ARF, dialysis may be required, especially in view of the hypercatabolic state of the patient. Plasmapheresis has also been successfully employed in patients with severe Weil’s disease.\(^11\) Nitric oxide inhalation along with respiratory care and continuous venous hemofiltration have been beneficial in one case.\(^12\)

According to the annual report of the Gilan University of Medical Sciences (Gilan, Iran), there has been a steady increase in the diagnosis of leptospirosis in recent years; 300 cases were registered in 2000.\(^13\) Because the clinical features and routine laboratory findings of leptospirosis are not specific, a high index of suspicion remains essential for the diagnosis. Although the organism can be cultured, the diagnosis is more frequently made by serological testing. In approximately 50% of patients blood cultures may become positive in the first 10 days of the illness. Urine culture becomes positive during the second week of the illness and remains positive for up to 30 days after resolution of the symptoms.\(^14\) The serological tests that are most often used for diagnosis include the microscopic agglutination test (MAT), macroscopic agglutination test, indirect hemagglutination, and enzyme-linked immunosorbent assay (ELISA).

The gold standard serological test has been MAT; however, the test requires live organisms and considerable expertise and is only performed in certain reference laboratories. In research performed by the Iran Pasteur Institute between 1999 and 2001 in Gilan Province in the north of Iran, 405 clinical cases of leptospirosis were tested with three different serological tests: MAT, ELISA, and an immunofluorescent (IF) method. They found that the sensitivity and specificity of the IF method to be 95% and 100%, respectively, as compared to the gold standard MAT test.\(^13\) It was concluded that a single IF titer $>1:100$ was strong evidence of current or recent infection with leptospira.

The clinical manifestations of infections are variable depending on the infecting pathogen, the prior immune status of the host, the time after transplantation, the level of pharmacological immunosuppression, and many other factors.\(^15\) The severity of leptospira infections ranges from a subclinical illness detected by seroconversion among persons with frequent exposure to leptospires to two clinically recognizable syndromes: a self-limited, systemic illness seen in roughly 90% of infections, and a severe, potentially fatal illness accompanied by any combination of renal failure, liver failure, and pneumonitis with hemorrhagic diathesis.\(^16\) Fever in the acute septicemic phase of leptospirosis is high and remittent (38°C to 40°C), with regard to the biphasic nature of leptospirosis (Figure 1).\(^17\) In Weil’s disease, a severe form of leptospirosis characterized by impaired hepatic and renal functions, patients developing severe disease manifestations may experience a 1- to 3-day improvement in fever and other constitutional symptoms that characteristically follows the acute-phase illness, or they may progress rapidly with high fever over 40°C and the onset of liver failure, ARF, hemorrhagic pneumonitis, cardiac arrhythmia, or circulatory collapse. In our case, the patient’s symptoms and signs took about 3 weeks before his

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**Fig 1.** Biphasic nature of leptospirosis and relevant investigations at different stages of disease. Specimens 1 and 2 for serology are acute-phase specimens; 3 is a convalescent-phase sample, which may facilitate detection of a delayed immune response; and 4 and 5 are follow-up samples that can provide epidemiological information, such as the presumptive infecting serogroup.
admission to the hospital. When he was admitted to the hospital, he had a combination of fever, headache, ARF, hyperbilirubinemia, and thrombocytopenia. Although myalgias occur in 80% of cases, our patient did not have any muscle tenderness, and creatinine kinase, lactate dehydrogenase, and aspartate aminotransferase levels were all normal. The patient’s urinary output was about 1.5 L/d. He did not use any drug(s) before his admission, except those mentioned (cyclosporine, prednisolone, azathioprine). After admission, and with regard to the patient’s history having walked barefoot in the rice farm, and leptospirosis endemic (the disease is also known by Iranian rice farmer as “rice’s fever”) the diagnosis of leptospirosis was made. At that time the serum leptospira antibody (IF) was positive (1/400; normal: < 1/100). This titer confirmed our diagnosis of leptospirosis. The definitive diagnosis of leptospirosis depends mainly on serological tests. The microscopic agglutination (MA) method is the reference standard serodiagnostic test; although useful as an epidemiological tool, this test is not sensitive enough to guide the diagnosis in time to influence the treatment of an individual case. According to Hatsadli et al’s study, immunofluorescent antibody (IFA) antibody can be detected earlier than the MA antibody, and the titers are higher. The IFA antibody first appeared during the first week of illness, reaching a peak by the fourth week, and then decreasing. The IFA titers were less than 1:400 after the fourth month.

The advantages of the IF test are as follows: 1) Since no specific treatment for different strains of leptospirosis exists and the attending physician is only interested in whether or not leptospirosis is present, he can be notified in a relatively short time whether a suspected case is positive or negative. 2) Because IF antibodies disappear earlier than agglutinating antibodies, a positive IF test almost always means fresh infection rather than an incidental finding of agglutinating antibodies in clinical cases resembling leptospirosis. It should be stressed that the IF test should serve only as a diagnostic procedure and not for epidemiological surveys, because in the MAT method there must be live leptospires. Due to its hazards to lab manpower, the MAT method was exclusively done only in The Basteur Institute for Research in Tehran, Iran. The cause of renal failure in this patient was directly related to infection with leptospirosis. Although, severe jaundice is one risk factor for the development of acute renal failure, especially when the total serum bilirubin exceeds 25 mg/dL. Hyperbilirubinemia in this case report (maximum total bilirubin in our patient was 23 mg/dL) could not be a direct cause of ARF. Several more recent placebo-controlled trials for leptospirosis, however, have demonstrated clinical efficacy of intravenous penicillin therapy in both severe and late disease. Even with advanced disease, intravenous penicillin decreases the duration of constitutional symptoms and the persistence of associated laboratory abnormalities and may prevent the development of leptospiruria. We started therapy with penicillin G, which took as long as 10 days. Azathioprine was temporarily withheld, and the patient was continued with prednisolone and reduced doses of cyclosporine.

Renal transplantation is increasing in developing countries. Some endemic infections, although not opportunistic, are more prevalent in certain geographic areas. Transplant physicians should be aware of the common endemic infections and diligently obtain an occupational exposure history of patients presenting with infectious complications and transplant dysfunction.

REFERENCES