Acute interstitial nephritis due to *Leptospira grippotyphosa* in the absence of Weil's disease

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Anicteric leptospirosis is a self-limited flu-like disease, whereas the icteric form is a severe illness characterized by multiple organ involvement or even failure. A case involving a patient with rapidly progressing renal insufficiency requiring intermittent renal replacement therapy due to *Leptospira grippotyphosa* in the absence of a Weil's disease is reported.

Key Words: Acute interstitial nephritis; *Leptospira grippotyphosa*; Morbus Weil

Leptospirosis, a zoonosis caused by spirochetes from the species *Leptospira interrogans* (divided into more than 200 serovars), occurs worldwide, but is far more common in tropical climates (1). Both wild and domestic animals can act as its host, and humans become infected from direct contact with the urine of an infected animal (where the organism is excreted) or from exposure to water, soil or other contaminated materials, through inhalation, ingestion or due to contact with abraded skin or mucosal tissues (2).

Leptospiral infections occur as two clearly identifiable clinical syndromes. Anicteric leptospirosis is self-limited, resembling a mild flu-like illness, whereas the icteric form, also known as Weil's disease, is characterized by severe systemic involvement, which may lead to multiple organ failure. The presentation is biphasic, with the acute, or septicemic phase, lasting approximately one week, followed by the immune phase, which is characterized by antibody production and excretion of leptospires in the urine. We report an unusual case of anicteric leptospirosis associated with a rapidly progressing renal insufficiency requiring intermittent renal replacement therapy, without any other major organ involvement, due to *Leptospira grippotyphosa*.

CASE PRESENTATION

A 26-year-old gymnastics teacher presented to the emergency department with a two-day history of elevated body temperature (39°C) with rigors, which began 96 h after returning from a month-long holiday in Thailand and Indonesia. He began his journey in Bangkok, Thailand, on July 29, 2011, where he stayed for two days, after which he continued backpacking north to Chiang Mai province, where he spent two days bamboo rafting (August 16 to 17, 2011); he reported ingesting water several times subsequent to falling from the raft. From there, he flew to Bali on August 19, 2011, where he spent the majority of his time at the beach. He noticed a cut, probably caused by a shell, on the sole of his left foot while swimming in the sea on the second day of his stay in Bali; he reported that he had been walking barefoot everywhere during his entire stay on the island. He returned to Switzerland on August 29, 2011.

The patient had received a booster immunization against tetanus and poliomyelitis and a vaccination for hepatitis A and B before he began his vacation.

La néphrite interstitielle aiguë causée par le *Leptospira grippotyphosa* en l'absence d'une maladie de Weil

La leptospirose anictérique est une maladie pseudogrippale spontanément résolutive, tandis que sa forme icterique est une maladie grave caractérisée par une atteinte multiorganique ou même par une insuffisance. Les auteurs présentent le cas d'un patient présentant une insuffisance rénale à évolution rapide exigeant une thérapie de substitution rénale intermittente attribuable à un *Leptospira grippotyphosa* en l'absence d'une maladie de Weil.

Otherwise, his medical and surgical history were not significant, apart from an atopic syndrome. He reported regular tobacco use (five to six cigarettes per day), but denied any alcohol or illicit drug use and was involved in a stable relationship.

The patient was well nourished and in good general condition. On admission, his temperature was 38°C, his heart rate was 70 beats/min, his respiratory rate was 12 breaths/min and his blood pressure was 123/72 mmHg.

A skin examination found a small wound, which had already formed a scar, on the sole of his left foot. The physical examination was otherwise unremarkable.

His white blood cell count was $7.9 \times 10^9/L$ (normal $4.0 \times 10^9/L$ to $10.0 \times 10^9/L$) with 78% neutrophils and his C-reactive protein level was 83 mg/L (normal <5 mg/L). The patient had a mild renal insufficiency (creatinine level of 116 $\mu\text{mol/L}$; creatinine clearance estimated using the Modification of Diet in Renal Disease formula 72 mL/min/1.73 m²) and a low blood sodium level of 133 mmol/L (normal 135 mmol/L to 145 mmol/L). A urine dipstick test showed only a minimal proteinuria without hematuria. A chest x-ray and an abdominal ultrasound did not show any abnormal findings.

Blood and urine cultures were negative. Serological tests for HIV, *Leptospira* species (<1 per 100), *Legionella pneumophila*, *Coxiella burnetii*, *Rickettsia conorii*, *Rickettsia mooseri*, *Salmonella* species and viral hepatitis, as well as a malaria immunological test and several thick blood smears, were all negative.

The initial therapeutic approach consisted of broad-spectrum antibiotic therapy with piperacillin-tazobactam and doxycycline. The clinical course was characterized by a persistent high-grade fever and the onset of a severe enteropathy with profuse, nonbloody diarrhea, which led to a broadening of the antibiotic treatment with the addition of ciprofloxacin and azithromycin. A decline in several laboratory parameters was observed including a mild anemia (hemoglobin level 118 g/L; normal 140 g/L to 180 g/L), an increase of the inflammatory state (C-reactive protein level 202 mg/L), a leukopenia ($3.8 \times 10^9/L$), a slight thrombocytopenia ($130 \times 10^9/L$; normal $150 \times 10^9/L$ to $450 \times 10^9/L$), a depression of the coagulation parameters (Quick 0.66; normal range 0.70 to 1.00) and a moderate cytolytic and cholestatic hepatopathy.

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(glutamate oxaloacetate transaminase 254 U/L [normal <41 U/L], glutamic-pyruvic transaminase 217 U/L [normal <41 U/L], gamma-glutamyltranspeptidase 283 U/L [normal 8 U/L to 61 U/L] and total bilirubin level 11.6 µmol/L [normal <19 µmol/L]).

There was development of a rapid progressive renal failure with oligoanuria and a sudden increase in all the kidney function tests (his creatinine level was 398 µmol/L after 48 h in hospital, 610 µmol/L after 72 h and 893 µmol/L after 120 h [normal <106 µmol/L]). A urine dipstick test was positive, with 10 to 20 leukocytes per field, >40 erythrocytes per field, some granular casts and epithelial cells.

These test results described an acute and rapidly progressing renal insufficiency, in association with a severe inflammatory state and an explosive enteropathy. The nephrological assessment consisted of several diagnostic tests: an immune screening ruled out an autoimmune disorder, and the levels of complement factors C3 and C4, and the results of the electrophoresis of seroproteins were both normal. A test for cryoglobulins was negative and fragmentocytes were not observed in a peripheral blood smear.

An ultrasound scan revealed an enlargement of both kidneys (right kidney 13 cm × 6.5 cm; left kidney 12 cm × 6.5 cm) in association with a hyperechogenicity of the cortex and provided confirmation of the absence of an obstructive nephropathy. The renal vascularization did not display any abnormal features.

A renal biopsy was performed as the next diagnostic step. The histological examination documented the presence of a tubulitis, associated with an infiltration of the interstitial space due to lympho-histioplasma cells (Figure 1). The immunohistochemical fixation showed several complexes of complement C5-9 and plasma cell deposits positive for immunoglobulin G and immunoglobulin M. The histological picture was consistent with an acute interstitial nephritis.

While these tests were being performed, renal function was supported for 11 days using short-term hemodialysis. A gradual recovery of kidney function, a resumption of diuresis with a subsequent polyuric phase and the onset of eosinophiluria were observed, confirming the diagnosis of interstitial nephritis. The measured creatinine clearance at discharge was 23 mL/min/1.73 m² (with a glomerular filtration rate of 17.4 mL/min/1.73 m²) and was 65.2 mL/min/1.73 m² at follow-up one month later.

In consideration of the precise travel history and the clinical picture, as well as the laboratory examinations, the patient was diagnosed with a leptospiral infection, and the decision to perform a second serological examination (microscopic agglutination test) was made. The results, which were obtained 10 days after admission, revealed an elevated titre for *L. grippotyphosa* (1:400 [normal <1:100]), and were confirmed by additional serological testing one month later (1:800 [normal <1 in 100]). In endemic areas, a titre of 1:100 or 1:200 is considered low, while a titre >1:400 is usually considered to be high; a fourfold rise in titre is the most definitive criteria for diagnosis of leptospirosis (3,4).

DISCUSSION

The intriguing aspect of the present case was the relatively mild clinical presentation, which did not include multiple major organ involvement, and the good general condition maintained by the patient, despite a rapidly progressing renal insufficiency, which required several days of short-term hemodialysis.

Renal involvement is very common in leptospiral infections (3-6), and ranges from a typically mild prerenal azotemia with anicteric disease (7,8) to severe renal insufficiency and subsequent failure, requiring dialysis, with Weil's disease, which is also associated with cholestatic jaundice, hyperbilirubinemia and a prolonged clinical course (9). All renal structures are pathologically involved. The main histological change is an interstitial nephritis, which is even observed in patients without clinical renal manifestations, whereas tubular necrosis is indicative of acute renal failure (10). The renal biopsy of the patient revealed the presence of a tubulitis associated with an infiltration of the interstitial space by lympho-histioplasma cells (Figure 1), which,

Figure 1) Renal biopsy specimen showing a tubulitis, associated with an infiltration of the interstitial space due to lympho-histioplasma cells

in agreement with histological descriptions in the literature, was consistent with an acute interstitial nephritis.

We excluded other causes of acute interstitial nephritis (hypersensitivity reaction due to drugs, immunological diseases, acute transplant rejection) based on the patient's history, and clinical and laboratory data.

After reviewing the entire clinical presentation, including the course of the disease, as well as the laboratory tests performed during the hospitalization period, it was evident that this particular case did not reflect the typical scenario of severe multiple organ disease in leptospirosis. The fact that the patient presented with an explosive enteropathy can simply be explained by the serovar *grippotyphosa*, which is known to be associated with gastrointestinal symptoms (11).

In addition to the present case, there are other published reports, caused by different serovars, involving cases of anicteric leptospiral renal failure without major hepatic involvement or hemorrhagic complications that experienced complete restoration of kidney function (12-14).

Clinicians should, therefore, consider the possibility of leptospirosis in the case of febrile illness followed by an acute renal failure, even in the absence of jaundice and other classical signs of Morbus Weil. This is particularly true if travel to an endemic area is associated with certain outdoor activities that carry an elevated risk of leptospiral infection. However, one cannot forget that leptospirosis is becoming an emerging global public health problem (15).

Southeast Asia is an endemic area for leptospirosis: of the serovars included in the major pathogenic species, 70% have been isolated in the Asian continent (16). However, the nonspecificity of the symptoms and signs of leptospirosis, and the high regional endemicity of other infectious diseases, such as malaria and dengue hemorrhagic fever, leads clinicians in Western countries to primarily consider a presumptive diagnosis other than leptospirosis even in the absence of conclusive laboratory testing. It is important to obtain an accurate travel history because this helps to determine the incubation period and the route of leptospiral acquisition. We know that ecotourism and adventurous recreational outdoor activities, such as river rafting, kayaking, canoeing, riding trail bikes through puddles and caving, are a rapidly expanding part of the travel industry (17,18), and that the potential exposure to leptospirosis through skin abrasions during such activities, as well as direct swallowing of contaminated water, is very high.

Leptospira are susceptible in vitro to a variety of antibiotics, including penicillins, cephalosporins, aminoglycosides and macrolides. The first choice of antibiotic therapy consists of the administration of intravenous penicillin for seven days; doxycycline is a good oral treatment alternative in less severe cases (19).

Besides antibiotic treatment, early and frequent dialysis is vital, because acute renal failure with major organ involvement has a poor outcome.

CONCLUSION

Severe acute kidney insufficiency can complicate anicteric leptospirosis, which challenges the notion that the renal disease associated with mild forms of leptospirosis is typically less severe and prerenal in nature.

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