Renal failure, hepatitis and myocarditis in a previously healthy man

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CASE PRESENTATION

A 32-year-old male migrant worker from St Lucia presented to the emergency department with a one-week history of myalgias, headache and fever. He was previously healthy. He was visiting Canada temporarily and had arrived in Canada 11 days before his presentation. One day after arriving in Canada, he ate commercially prepared hamburger patties, which he reported as "off-tasting". Five days later, he became fatigued and experienced a bilateral, intermittent headache associated with photophobia and visual aura. He noticed that his eyes were bloodshot. Three days later, he developed loose, nonwatery, non-bloody diarrhea, associated with fever and rigors, which resolved completely in two days. At presentation, he complained of lethargy, lower-extremity myalgias, tea-coloured urine and intermittent epigastric discomfort. On examination, his temperature was 37.2°C, heart rate 87 beats/min, respiratory rate 18 breaths/min and blood pressure 113/72 mmHg. He had scleral icterus with conjunctival edema (Figure 1). He had no hepatosplenomegaly. His leukocyte count was $19.9 \times 10^9/L$, hemoglobin level 124 g/L and platelet count $24 \times 10^9/L$. His electrolyte levels, bicarbonate levels and anion gap were within normal limits; however, his creatinine level was 352 $\mu\text{mol/L}$ and urea level was 18 mmol/L. His aspartate aminotransferase level was 310 U/L, alanine transaminase level 175 U/L, alkaline phosphatase level 79 U/L and total bilirubin level 191 $\mu\text{mol/L}$. His initial creatine kinase level was 2343 U/L and troponin I level was 1.6 $\mu\text{g/L}$. An initial electrocardiogram showed sinus rhythm with first-degree atrioventricular block and an incomplete right bundle branch block.

He was admitted with an initial, presumptive diagnosis of hemolytic uremic syndrome or thrombotic thrombocytopenic purpura, and received two units of fresh frozen plasma. A hemolysis work-up returned negative: serum lactate dehydrogenase level was 353 U/L, haptoglobin level 2.9 g/L, total bilirubin level 191 $\mu\text{mol/L}$, indirect bilirubin level 60 $\mu\text{mol/L}$ and direct bilirubin level 131 $\mu\text{mol/L}$. On a blood film, fragments were only rarely observed. Abdominal ultrasonography revealed hepatic periportal echogenicity, diffuse renal cortical echogenicity and no hydronephrosis. Echocardiography showed mild concentric left ventricular wall thickening and no regional wall motion abnormalities, with a preserved left ventricular ejection fraction (54%). Furthermore, serology for cytomegalovirus, hepatitis A virus, hepatitis B virus, hepatitis C virus and HIV were negative. Blood films failed to show intraerythrocytic trophozoites. Blood cultures were negative. Stool culture for *Escherichia coli* O157:H7 was also negative.

He remained clinically stable and had good urine output with improving kidney function. However, his leukocyte count increased to $37.6 \times 10^9/L$ and his direct bilirubin level and erythrocyte sedimentation rate increased to 169 $\mu\text{mol/L}$ and 110 mm/h, respectively, suggesting progression of his hepatopathy and ongoing systemic inflammation.

A diagnostic test was performed.

DIAGNOSIS

Leptospirosis serology was ordered.

The present case contains many classic features of severe icteric leptospirosis. Jaundice, headache, conjunctival suffusion, myalgias and diarrhea are all common symptoms (1). In severe leptospirosis, a peripheral leukocytosis with left shift occurs. There tends to be a direct hyperbilirubinemia with lesser increases in transaminase levels and slight elevation of alkaline phosphatase levels, which appear to be related to the cholestasis of sepsis. Clinical and biochemical rhabdomyolysis is common (2). Electrocardiographic abnormalities are frequent, including first-degree atrioventricular block and widespread T-wave inversion (3). Leptospirosis-associated myocarditis confers a case mortality rate as high as 54% (1). Severe thrombocytopenia can occur, but this is less common and indicates a poorer prognosis (2).

After serum was obtained, the patient was started on intravenous benzylpenicillin 3×10^6 units every 6 h. He quickly improved clinically. Three days later, he was discharged home on ceftriaxone 1000 mg intravenously daily for a total of 14 days. Three weeks postdischarge, the patient was seen in the outpatient clinic and was clinically well. His creatinine level normalized to 92 $\mu\text{mol/L}$. His leukocyte count was $8.2 \times 10^9/L$, hemoglobin level 109 g/L and platelet count was $441 \times 10^9/L$. His liver enzyme levels remained mildly elevated (alanine transaminase 147 U/L and alkaline phosphatase 200 U/L). Retrospectively, the patient reported wading in fresh water while in St Lucia two weeks before his presentation to the authors' hospital as well as seeing rodents around his house.

The serum was sent to the National Microbiology Laboratory in Winnipeg, Manitoba. Leptospirosis ELISA for immunoglobulin M was found to be positive using the Panbio *Leptospira* IgM ELISA (Inverness Medical Innovations Australia Pty Ltd, Australia). Interpretation criteria were as follows: <9 Panbio units, unreactive; 9 to 11, equivocal; and >11, positive. ELISA results were confirmed using a microagglutination test beginning at a screening dilution of 1:100. Further testing revealed *Leptospira interrogans* serovar Autumnalis as the most likely serovar (titre 1:800).

DISCUSSION

Leptospirosis is a worldwide zoonotic infection caused by spirochetes of the genus *Leptospira* (2). The estimated incidence of leptospirosis ranges from 0.1 per 100,000 to 100 per 100,000, with tropical regions having the highest incidence (4). The disease reservoir is maintained in carrier animals through persistent colonization of their proximal renal tubules. Animals, including humans, can be asymptomatic carriers. Mice, among other mammals, are important sources of transmission and excrete *Leptospira* in their urine (2). Human infection occurs by exposure to this urine either directly or via fresh-water contamination. Human-to-human transmission is extremely rare (1). Bacteria can infect humans through abrasions or cuts in the skin or direct ingestion of contaminated water (5). Higher-risk activities include

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Figure 1) Photograph of the eyes of a 32-year-old man who presented with myalgias, headache and subjective fever. Scleral icterus with conjunctival edema is evident. His total bilirubin level was 256 $\mu\text{mol/L}$ when this photograph was taken

fresh-water bathing, fishing and canoeing (6). Several cases of leptospirosis have been reported in the returning traveller (5,6).

Infection can generally be divided into two categories: icteric and nonicteric leptospirosis. The icteric form is more severe and is also known as Weil's disease. This usually presents as rapidly progressive jaundice, renal failure and hemorrhagic sequelae with a variable clinical course. Intra-alveolar and interstitial pulmonary hemorrhage is most commonly observed. Diagnosis depends on a high clinical suspicion because results of serological tests generally take at least one week to return. Treatment of icteric leptospirosis remains controversial due to limited data. However, the WHO strongly recommends early treatment with antibiotics for severe leptospirosis (4). In a systematic review including 403 patients randomly assigned in four trials to receive parenteral penicillin versus placebo, penicillin reduced the length of clinical disease, but there were no differences between penicillin and placebo in all-cause mortality or length of hospitalization (7). Further trials showed no superiority of penicillin compared with cephalosporins or doxycycline (7).

Similar to antibiotic treatment of other spirochetal infections, there is a rare risk of a Jarisch-Herxheimer reaction with treatment. This reaction is caused by the host inflammatory response to endotoxins released when there is rapid widespread bacterial lysis. It typically occurs within 2 h of treatment and presents as fever, chills, rigors, hypotension and tachycardia (3). Most patients with icteric leptospirosis will recover without long-term sequelae.

CONCLUSION

Leptospirosis is a global zoonotic disease with potentially deadly consequences if not recognized. Acute-onset jaundice, renal failure and pulmonary hemorrhage, especially in a patient travelling from a tropical area, should raise concerns about leptospirosis, especially if initial malaria testing returns negative.

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