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BRIEF REPORT

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Massive rhabdomyolysis and multiple organ dysfunction syndrome caused by leptospirosis

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Abstract We report a case of leptospiral infection in a 63-year-old man who acquired the infection while swimming in canals and streams in Hawaii. The patient's course was atypical in that he was anicteric and had no evidence of meningitis when he presented with fever, rapidly progressive and severe rhabdomyolysis, thrombocytopenia, acute renal failure, and respiratory distress syndrome. Although he recovered after a protracted illness, he required major life support, including mechanical ventilation and hemodialysis. Initial antimicrobial therapy was designed to cover major bacterial and atypical pathogens, including leptospires. An in-depth work-up for causes of this catastrophic illness confirmed acute leptospirosis. Although rare, leptospirosis is a potentially lethal infection classically associated with hepatitis, azotemia, and meningitis. Most patients experience self-limited illness, with fever, myalgias, and malaise followed by an immune-mediated aseptic meningitis. A small proportion develop shock and multiple organ dysfunction. Whereas myalgias are ubiquitous in leptospiral infection, and most patients show mildly elevated muscle enzymes, life-threatening rhabdomyolysis is rare. This atypical case is reported to urge clinicians to consider leptospirosis in the evaluation of a patient with cryptogenic sepsis who develops multiple organ dysfunction associated with rhabdomyolysis. Appropriate antimicrobial therapy, with penicillin or doxycycline, can be life-saving.

Keywords Acute renal failure · Acute respiratory failure · Atypical pneumonia · Leptospirosis · Multiple organ dysfunction syndrome · Rhabdomyolysis ·

Introduction

Leptospirosis is a ubiquitous spirochetal zoonosis which afflicts 40–120 patients each year in the United States [1]. Although most often acquired occupationally, from contact with infected animals, leptospirosis is being increasingly seen in persons who acquired the infection through exposure to contaminated water [2]. Leptospires are excreted in the urine of infected animals; their survival is enhanced by temperatures higher than 22 °C, a moist environment, and alkaline soil [1]. Leptospiral infections occur primarily in tropical climates or during the warm months in temperate areas of the world. Documented cases have been reported from all continents except Antarctica.

We report a case of severe leptospirosis in a previously healthy man who acquired the infection while vacationing in Hawaii but became ill only after returning to Wisconsin. His presentation and course were unusual: despite rapidly progressive multiorgan dysfunction, he remained anicteric and never manifested signs of meningitis, but rather exhibited massive rhabdomyolysis with severe thrombocytopenia, acute renal failure, and acute respiratory distress syndrome (ARDS).

Table 1. Selected laboratory findings (hospital days 1–7, 30) in a case of severe leptospirosis with rhabdomyolysis and multiorgan dysfunction (*AST* aspartate aminotransferase, *PEEP* positive end-expiratory pressure, *CPAP* continuous positive airway pressure, *FM* face mask, *BiPAP* bilevel positive airway pressure, *PS* pressure support, *A/C* assist-control)

HOSPITALS DAY	1	2	3	4	5	6	7	30
White Blood Count ($\times 10^9$/L)	24	16	17	21	19	14	8	
Platelet Count ($\times 10^9$/L)	12	5	14	15	26	40	90	261
Transfused Platelets (no. of units)	6	12	6	6	6			
Creatinine (micromol/L) (normal = 53–133 micromol/L)	702	820	540	550	600	780	810	260
Creatinine Clearance (mL/L)	1				8			22
AST (microKat/L) (normal = 0.17–0.67 microKat/L)	9.1		2.4		1.3	0.9		
Creatinine Kinase (microKat/L) (normal 1.0–6.7 microKat/L)	430	668	230	110	20	6.2		
PaO_2/FiO_2	160	137	182	200	220	240	264	
Mode of Ventilation* * FM = Face Mask, CPAP = Continuous Positive Airway Pressure BiPAP = BilevelPAP PS = Pressure Support A/C = Assist-Control	FM CPAP BiPAP intubated A/C	A/C CPAP	A/C	A/C	A/C	PS/CPAP	PS/CPAP FM extubated	
PEEP or CPAP (mmH_2O)	10	10	8	8	5	5	5	

Case report

A previously healthy and vigorous 63-year-old man developed fever, chills, nausea, vomiting, and myalgias, most notable in his calf muscles, 3 days prior to admission to an outside hospital. He had no pets and was unaware of toxic exposures or ingestion of undercooked meat. He had returned from a family vacation in Hawaii 10 days prior to the onset of illness, where he had kayaked and swum in the ocean, canals, and streams. His past medical history was remarkable for mild type II diabetes, well controlled with glyburide.

At the time of admission he was profoundly dehydrated, and lower extremity myalgias and weakness were so severe that he was unable to walk. He was found to be anemic, thrombocytopenic, and oliguric and had a markedly elevated creatine kinase (CK) with myoglobinuria. Shortly thereafter he was transferred to the University of Wisconsin Center for Trauma and Life Support.

On presentation the patient's temperature was 38.2 °C, heart rate 107 beats/minute, respiratory rate 30 breaths/minute, and blood pressure 164/79 mmHg. He was alert and oriented, anicteric, and showed no evidence of conjunctival injection or suffusion but diffuse petechiae were present over his entire body. Dry crackles were audible throughout both lung fields, but heart sounds were normal. He had minimal abdominal tenderness with increased bowel sounds, but no guarding or tenderness. The liver spanned 8 cm and was nontender; the spleen was not palpable. He had no meningismus and was intact neurologically but exhibited exquisite tenderness of his gastrocnemius, soleus, and anterior dorsiflexor muscles bilaterally; the lower extremity compartments, however, were soft and nontender. Muscle strength in his lower extremities, was 4/5, and deep tendon reflexes were normal.

Laboratory studies on admission to our center (Table 1) showed a blood urea nitrogen of 38 mmol/l (106 mg/dl), creatinine 702 μmol/l 8.0 mg/dl), hematocrit 0.21 (21 %), platelet count 12×10^9/l, white blood cell count 17.4×10^9/l with a mild shift to the left, international normalized ratio 1.0, haptoglobin 2.0 g/l (200 mg/dl), sodium 124 mmol/l, potassium 4.6 mmol/l, chloride 91 mmol/l, bicarbonate 14 mmol/l, glucose 8.5 mmol/l (174 mg/dl), aspartate aminotransferase 9.1 μKat/l (548 U/l), alanine aminotransferase 4.1 μKat/l (274 U/l), total bilirubin 7 mmol/l (0.4 mg/dl), alkaline phosphatase 1.7 μKat/l (104 U/l), lactic dehydrogenase 7.7 μKat/l (774 U/l), and CK 430 μKat/l (25,800 IU/l). The urine was positive for myoglobin. The peripheral blood smear showed very few platelets and rare schistocytes. Electrocardiography showed sinus tachycardia. Chest radiography showed a normal cardiac silhouette with diffuse bilateral air-space disease (Fig. 1). Abdominal radiography was normal. Urinalysis revealed isosthenuria, myoglobinuria, and granular casts. The initial creatinine clearance was 1 ml/min.

Infectious diseases, nephrology, and hematology consultants evaluated the patient. Bacterial cultures of blood, urine, and sputum were obtained, and he was begun on ceftriaxone, trimethoprim-sulfamethoxazole, and doxycycline.

CK continued to increase for several days after transfer and peaked at 668 μKat/l (40,000 IU/l; Table 1). A double-lumen internal jugular catheter was inserted, and hemodialysis was initiated. However, despite ultrafiltration he became increasingly hypoxemic and showed worsening of bilateral air-space disease (Fig. 1, Table 1). Ventilation was initially supported with nasal bilevel positive airway pressure (BiPAP, Respironics, Murraysville, Pa., USA), but the patient subsequently required intubation and mechanical ventilatory support, using a volume assist-control mode.

Investigations were undertaken at the outset to identify an autoimmune disease or infectious cause of his illness, including leptospirosis (Table 2). Anti-nuclear, anti-DNA, anti-neutrophil cytoplasmic and anti-glomerular basement membrane antibodies were not detected. Bronchoalveolar lavage was negative for infectious causes of respiratory failure, including *Pneumocystis carinii* pneumonia. Because of severe thrombocytopenia, bone marrow biopsy was performed and showed normal cell lines with increased cellularity; bacterial, fungal, and viral cultures were negative.

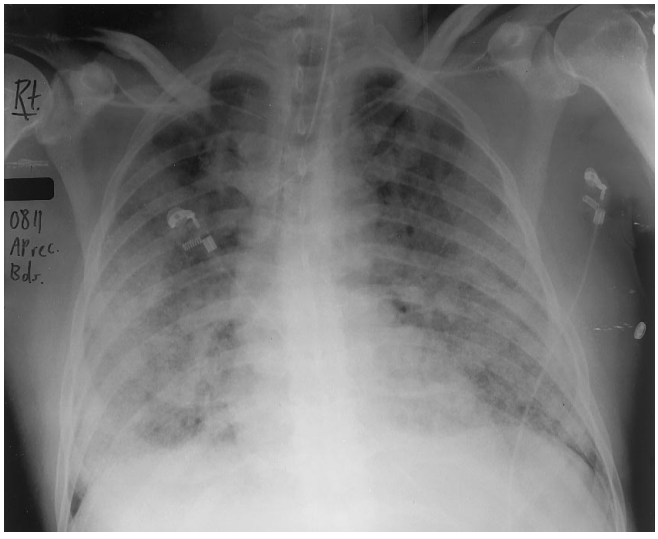

Fig. 1 Chest radiography. Normal cardiac silhouette with diffuse bilateral air-space disease

All of the diagnostic studies for infectious causes were unrevealing (Table 1) with the exception of a leptospiral titer by microscopic agglutination test (MAT), carried out at the Centers for Disease Control (Atlanta, Ga, USA); the titer increased from 1:100 on day 1 to higher than 1:6400 on day 21.

The patient's respiratory status gradually improved, and 7 days after admission he was successfully weaned and extubated (Table 1). He was transferred to his home hospital on the 24th hospital day and ultimately made a complete recovery. He is now well, dialysis-free, and working full time less than 2 years following his near-fatal catastrophic illness.

Discussion

Leptospirosis is a biphasic illness with two stages, septicemic and immune. The septicemic phase, which lasts 3–7 days, is heralded by sudden fever with rigors, headache, profound myalgias, dehydration, and often cardiovascular instability [1]. Defervescence and symptomatic improvement follows; however, as IgM antibodies appear, the immune stage ensues, with aseptic meningitis the hallmark clinical feature in 70–96 % of reported cases [3]. Infection occurs within several days to as long as 4 weeks following exposure [1, 2].

Two distinct clinical syndromes are encountered in leptospirosis; 90 % of patients experience a relatively mild, self-limited, anicteric febrile illness. A far smaller proportion, 5–10 %, develop icteric leptospirosis, or Weil's syndrome, which is far more severe and potentially lethal, and is characterized by hepatic, renal, and cardiovascular dysfunction with meningitis. With appropriate antimicrobial therapy and optimal supportive care, mortality is in the range of 5–10 % [1]. Most patients are jaundiced although the maximum serum bilirubin level rarely exceeds 340 mmol/l (20 mg/dl). Higher levels can be seen with severe infection and are associated with a high incidence of acute renal failure. Hepatomegaly is reported in 25 % of patients, but transaminase levels are rarely elevated above three times the upper limit of normal [1, 2]. Isolated thrombocytopenia, not associated with disseminated intravascular coagulation, develops in 50 % of patients with leptospirosis, reflecting a generalized microvasculitis associated with a systemic hemorrhagic diathesis, and is closely correlated with the occurrence of renal failure and a poorer prognosis [4].

Table 2. Studies to Identify Infection (*MAT* microscopic agglutination test, *DFA* direct flurorescent antibody, *IFA* indirect fluorescent antibody, BAL bronchoalveolar lavage, *MIF* microscopic immunofluorescence, *ELISA* enzyme linked immunoabsorbent assay)

INFECTIOUS AGENT	TESTS	RESTULTS
Leptospires	Serologic (MAT*)	Positive
Conventional Aerobic and Anaerobic Bacteria	Multiple cultures and gram stains	Negative
Legionellae	Serologic (DFA**), sputum culture, urine antigen	Negative
Chlamydiae	Serologic (MIF††)	Negative
Rickettsia	Serologic (IFA***)	Negative
Erlichiae	Polymerase chain reaction	Negative
Epstein-Barr virus	Serologic (ELISA†††)	Negative
Hanta virus	Serologic (ELISA)	Negative
HIV	Serologic (ELISA)	Negative
Cytomegalovirus	BAL† and blood shell-vial cultures	Negative
Respiratory viruses	BAL† and stool cultures	Negative
Enteroviruses	Stool cultures	Negative
Pneumocystis carinii	BAL† and gomori-methenamine-silver	Negative

* MAT microscopic agglutination test:
L. icterohaemorrhagiae: acute titer 1 : 100; convalescent 1 : 6400
L. copenhageni M20: acute 1 : 100; convalescent 1 : 6400
L. manakrso: acute negative; convalescent 1 : 3200
** DFA – direct fluorescent antibody
*** IFA – indirect fluorescent antibody
† BAL Broncho-alveolar lavage
†† MIF – microscopic immunofluorescence
††† ELISA – enzyme linked immunoabsorbent assay

Our patient's course was atypical because he was anicteric, had no conjunctival inflammation and never showed evidence of meningitis but rather developed acute life-threatening multiple organ dysfunction and, most strikingly, severe rhabdomyolysis (Table 1). His clinical presentation was initially most suspicious for an autoimmune disease, such as acute systemic lupus erythematosus, polyarteritis nodosum, Wegener's granulomatosis, or Goodpasture's syndrome. However, these conditions were quickly excluded. With fever, rapidly progressive renal failure, and profound thrombocytopenia, thrombotic thrombocytopenic purpura or hemolytic uremic syndrome were also suspected. However, the patient never showed evidence of neurological disease or microangiopathic anemia, his serum haptoglobin level was normal, and his lactic dehydrogenase never rose above twice the upper limit of normal; moreover, severe rhabdomyolysis would have been very unusual with thrombotic thrombocytopenic purpura or hemolytic uremic syndrome.

A wide variety of infections which could have caused this unique systemic illness were also considered at the outset and sought diagnostically, including bacterial sepsis, leptospirosis, legionellosis, mycoplasma infection, hepatitis A or B, influenza A, and infection by other respiratory viruses, Epstein-Barr virus, cytomegalovirus, human immunodeficiency virus, hantavirus, and *P. carinii*, but an exhaustive workup excluded all with the exception of leptospirosis (Table 1).

Leptospirosis can be diagnosed by recovery of the organisms in culture of urine, blood, or cerebrospinal fluid but requires special media and prolonged incubation [5]. Recent studies suggest that the use of polymerase chain reaction for detection of leptospiral DNA is a promising rapid and highly accurate diagnostic technique [6]. Most cases of leptospirosis, as ours, are diagnosed serologically using the gold standard, MAT [1, 2, 5]: a fourfold rise in convalescent titer or a single titer of 1:800 or higher is considered diagnostic [5]. In our patient, cultures were not carried out because of the unavailability of special media and the urgency of beginning anti-infective therapy.

Our patient's travel history and aspects of his clinical picture pointed towards atypical leptospirosis from the outset, especially when it was learned that while in Hawaii, the patient and his family had kayaked through a series of irrigation canals, and the patient was the only member of his family to swim at a waterfall and pool that had been implicated in Hawaiian cases of leptospirosis. The highest incidence of leptospirosis in the United States is in Hawaii, where the annual rate (128 per 100,000) is more than 100 times higher than in the continental states [1, 2]. The patient's potential exposures 2 weeks prior to the onset of illness makes it very likely that he acquired his infection in Hawaii but became ill only upon returning to his home in Wisconsin.

The diagnosis of leptospirosis was confirmed serologically 4 weeks after the onset of his acute illness, but his initial antimicrobial regime, which included ceftriaxone and doxycycline – designed to cover common bacterial as well as atypical pathogens – is highly active against leptospires [7]. Although intravenous penicillin is considered the treatment of choice for leptospirosis [1, 8], doxycycline has been shown to be effective in clinical trials [9] and is more effective than penicillin for prophylaxis [1].

Our patient had moderately severe ARDS by the criteria of the American Thoracic Society–European Society for Intensive Care Medicine ($PaO_2/FIO_2 < 200$ in the absence of heart failure). Atypical pneumonia or ARDS is a frequent concomitant in severe leptospirosis and usually occurs in icteric patients; pulmonary lesions have been found to be primarily hemorrhagic rather than inflammatory [10]. Patients with leptospiral pneumonia are considered to be at increased risk for secondary pyogenic bacterial pneumonia.

Acute renal failure develops in 15–63 % of patients with leptospirosis and portends increased morbidity and mortality [11]. The wide variability in the incidence of acute renal failure has been ascribed to use of different criteria. About 15 % of patients develop azotemia and oliguria unresponsive to rehydration or furosemide. However, hyperkalemia is uncommon in patients with leptospiral-induced renal failure, which is surprising considering the catabolic state and rhabdomyolysis characteristic of severe infections. Renal failure appears to be multifactorial, from dehydration, myoglobinuria, and jaundice. Acute interstitial nephritis is most often seen histologically [10].

Nearly all patients with acute leptospirosis experience severe myalgias, and most show laboratory evidence of mild rhabdomyolysis [12]; severe rhabdomyolysis, however, while reported [13], is fortunately rare. Elevation in the CK in a jaundiced patient with mild to moderate elevation in serum transaminases should always raise the consideration of leptospirosis rather than viral hepatitis. The etiology of rhabdomyolysis in patients with leptospiral infections remains to be elucidated. Speculation has focused on spirochetal release of an exotoxin which damages muscle directly or invasion of the leptospires into muscle resulting in inflammation and destruction [13].

In conclusion, when faced by a critically ill patient with fever, pulmonary infiltrates, renal failure, and rhabdomyolysis, leptospirosis must be considered, even in the absence of jaundice or meningitis, especially if there is a history of exposure to fresh water or contact with animals – dogs, rats, cattle, or pigs. Antimicrobial therapy should not be withheld while awaiting diagnostic tests and should include penicillin or doxycycline.

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