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CASE REPORT

Leptospirosis with transient paraparesis and thrombocytopenia: A case report

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Leptospirosis is the most widespread zoonosis in the world. We present an unusual case of leptospirosis in a 44-year-old man with severe thrombocytopenia and transient paraparesis. The diagnosis of leptospirosis was confirmed by blood nested polymerase chain reaction, sero-conversion of *Leptospira* IgM and the microscopic agglutination test. Nerve conduction studies were suggestive of early polyneuropathy involving the right peroneal nerve and bilateral sural nerves. Peripheral nerve palsy is a potential clinical feature of leptospirosis. Copyright © 2011, Taiwan Society of Microbiology. Published by Elsevier Taiwan LLC. All rights reserved.

Introduction

Leptospirosis is an important zoonosis of worldwide distribution, predominantly involving tropical and rural areas. The clinical spectrum of the disease ranges from an asymptomatic, subclinical anicteric leptospirosis manifesting as an influenza-like presentation of fever and myalgia, to a fatal hepatorenal syndrome, well known as Weil's

disease, comprising jaundice, renal dysfunction, and bleeding diathesis.¹ Thrombocytopenia is commonly observed in severe leptospirosis.² However, it is uncommon for leptospirosis to present as a primary neurological disease.³ Here, we present a case of leptospirosis with severe thrombocytopenia and polyneuropathy involving the right peroneal nerve and bilateral sural nerves mimicking myeloradiculopathy, which is rarely encountered clinically.

Case report

A 44-year-old man was admitted to our hospital via the emergency department because of fever and general

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malaise for a few days. He denied a history of systemic disease, except for psychiatric disorder that was under regular medical control. He was in his usual state of health until several days before this admission, when he developed subjective fever, followed by back pain with bilateral leg weakness, cough and general malaise. He was sent to a local hospital where, at first, discitis was suspected clinically, and he was transferred to our hospital. He also complained of diarrhea and abdominal pain on percussion. He worked as a fish-seller, and had sometimes been injured by fish. There was no past history of diabetes or hypertension, nor any recent travel history. No other family members reported being sick recently. Besides, he had been involved in a traffic accident 4 months before this admission.

At the emergency department, he was dyspneic and hypotensive (blood pressure 87/40 mm Hg). He had paraparesis (grade 2/5 of motor power), and no sensory or bladder abnormalities. Examination of cranial nerves and cerebellar system did not reveal any remarkable findings; there were no meningeal signs. The results of laboratory testing were as follows: hemoglobin level 14.4 g/dL; white blood cell count 9140 cells/mL; bandemia (band form neutrophils: 25–52%); platelet count 18,000/mL (nadir at 10,000/mL); C-reactive protein 16.39 mg/dL; fibrinogen 282.9 mg/dL and D-dimer 2947.74 ng/mL; blood urea nitrogen 31 mg/dL; serum creatinine 2 mg/dL; sodium 133 meq/L; potassium 3.4 meq/L; serum calcium 1.69 mmol/L; inorganic phosphorus 3.4 mg/dL; total bilirubin 2.0 mg/dL; direct bilirubin 1.1 mg/dL; aspartate aminotransferase 228 IU/L; alanine aminotransferase 70 IU/L; serum total protein 4.9 g/dL; albumin 2.4 g/dL; amylase 313 IU/L; lipase 212 IU/L; creatinine phosphokinase 4148 U/L; creatinine kinase-MB 63 IU/L; troponin I 0.21 µg/L; and lactate dehydrogenase 434 IU/L. Lumbar puncture was not done because of bleeding tendency. Urinalysis showed 1+ proteinuria, microscopic hematuria (red blood cells: 35–40/high power field, occult blood: 4+), and mild pyuria (white blood cells: 3–5/high power field, pus cells: 1+). Urine and blood cultures were all sterile.

Considering his occupational exposure combined with acute renal and hepatic insufficiency, leptospirosis or Weil's disease was suspected and penicillin was given. Dopamine with normal saline and platelet transfusion were given to support his blood pressure and prevent spontaneous bleeding. Then, he was admitted to our medical intensive care unit for further care. Intravenous cotrimoxazole was subsequently added to the antibiotic regimen to treat possible *Staphylococcus aureus* discitis. Respiratory distress was treated with bi-level positive airway pressure and methylprednisolone (40 mg every 8 hours). Chest X-ray showed cardiomegaly and increased interstitial infiltration of both lungs, consistent with pulmonary vascular congestion. Patchy consolidation in bilateral lungs was suspicious for active infectious process (Fig. 1). Intravenous fluids were reduced due to congested lung on the fourth day in hospital, and methylprednisolone was tapered to 20 mg every 12 hours on the sixth day in hospital. Acute serum *Mycoplasma pneumoniae* antibody was negative (<1:40), IgM antibodies for *Leptospira* detected with indirect hemagglutination test (Focus Diagnostics, Cypress, CA, USA; associated with 92% sensitivity and 95% specificity),



Figure 1. Chest X-ray showed enlarged heart size, patchy consolidation in both lungs, and increased interstitial infiltration of both lungs, suggesting pulmonary congestion.

and the microscopic agglutination test (MAT) was negative. High-dose methylprednisolone therapy resulted in a dramatic improvement of thrombocytopenia, pneumonia and resulting acute respiratory distress syndrome. His blood pressure became normal and dopamine was tapered and discontinued, and he had no weakness or numbness of both legs by the second day in hospital. He was then transferred to a medical ward with stable vital signs.

After he was transferred to our ward, magnetic resonance imaging of the lumbar spine was normal, and discitis excluded. Intravenous cotrimoxazole was switched to levofloxacin on the seventh day in hospital to cover most respiratory pathogens, including *Mycoplasma* and other atypical microorganisms. Nerve conduction studies were suggestive of early polyneuropathy of the right peroneal nerve and bilateral sural nerves. Intravenous methylprednisolone and levofloxacin were discontinued on the 10th and 14th days in hospital, respectively. Gallium scan showed no remarkable findings. C-reactive protein declined to 0.30 mg/dL and complete blood count became normal with no bandemia after treatment. He was discharged in an ambulatory state with a normal platelet count of 205,000/µL. Other laboratory data, including fibrinogen, creatinine, liver function tests, amylase, lipase, cardiac enzymes, and lactate dehydrogenase all returned to normal. A convalescent serum sample obtained 2 weeks from the date of collection of the first sample showed that *M. pneumoniae* antibody was 1:160, IgM antibody for *Leptospira* was weakly positive, and the MAT showed seroconversion with significant antibody titers for *Leptospira shermani* (1:3200) and *Leptospira bataviae* (1:400). Blood

nested polymerase chain reaction (PCR) demonstrated *Leptospira interrogans*.

Discussion

Leptospirosis is a disease caused by spirochetes of the genus *Leptospira* and remains a challenge for clinicians, presenting high morbidity and mortality in selected cases.² The leptospires are transmitted through direct or indirect contact with infected animals or their urine.⁴ Typical manifestations include sepsis, acute renal failure, hepatic dysfunction, electrolyte imbalance, pulmonary hemorrhage, cardiovascular collapse, thrombocytopenia, pancreatitis, myocarditis, rhabdomyolysis, acalculous cholecystitis, purpuric skin lesions, pericarditis, and reactive arthritis.⁵ Thrombocytopenia is the most common hematological manifestation in severe forms of leptospirosis. Unusual clinical manifestations may result from immunological phenomena and involvement of pulmonary, cardiovascular, neural, gastrointestinal, ocular and other systems, and can cause fetal loss in pregnancy.⁶

Neuroleptospirosis can present as any of the following manifestations: cerebrovascular accident, cerebral venous thrombosis, cerebral arteritis, subarachnoid hemorrhage, blindness due to uveitis, optic neuritis, transverse myelitis, cranial nerve palsy, Guillain–Barré syndrome (GBS), mononeuritis multiplex, peripheral nerve palsy, psychosis, suicidal behavior, cerebellitis, encephalitis, meningitis, chronic meningitis, and primary meningitis.⁷ We have reported an interesting case of neuroleptospirosis presenting as *Leptospira* brain abscess and endocarditis complicated with cardiac aneurysm and multiple infarcts of brain, liver and kidneys, in association with *S. aureus* bacteremia.⁸ We have also observed cases of neuroleptospirosis presenting as seizures, migraine headaches, multiple sclerosis, ataxia, carpal tunnel syndrome, radiculopathy and Tolosa–Hunt syndrome.⁹ Deeply altered sensorium at presentation indicates poor prognosis.¹⁰

Common presentations in neuroleptospirosis are asymptomatic meningitis and encephalitis, and paraparesis due to myelitis or radiculopathy is very rare.^{3,6} Leptospirosis with sudden-onset paraparesis was reported in a 26-year-old woman 1 week postpartum, who presented with acute renal failure with hyperkalemia after a febrile illness with diarrhea.¹¹ GBS presenting as renal failure and ascending polyneuropathy had been reported following infection with *Leptospira icterohaemorrhagiae* in a 65-year-old woman,¹² and presumed infection with *Leptospira* serovar Copenhageni in a 12-year-old girl.¹³ Fatal leptospirosis presenting as jaundice, renal failure and flaccid paraplegia has also been reported.¹⁴ Most reported cases of neuroleptospirosis have been diagnosed only on the basis of IgM serology, without any information regarding the probable identity of the infecting serovar.^{3,14} In the present report, MAT titers were suggestive of a recent leptospiral infection with highest serovar against *L. shermani*, but nested PCR confirmed infection with *L. interrogans*. The MAT is the reference standard test for serological diagnosis of leptospires, and was carried out at Taiwan Centers for Disease Control by using representative serovars including Australis, Bratislava, Icterohaemorrhagiae, Kenne-wicki, Poi, Shermani, and Tarassov. Because

one serovar may belong to more than one species and members of the same genetic group do not necessarily belong to the same serogroup, *Leptospira* isolates should be characterized by both molecular and serological approaches.² In a large case series that reviewed culture-positive cases, it was not possible to predict the infecting serogroup in more than half the cases.¹⁵ Moreover, more than two serovars shown by MAT has been reported in GBS in a pediatric patient following infection due to *Leptospira*.¹³

The pathogenesis of neuroleptospirosis is not clear, but GBS is thought to be induced by molecular mimicry, toxin, or immune dysregulation.¹⁶ Molecular mimicry has been suspected to play a role in infection-induced GBS.¹⁷ Immunological phenomena secondary to antigenic mimicry have also been reported as an important component of many clinical features in leptospirosis.⁶ Antibodies generated in response to leptospiral infection may cross-react with host antigens, and may be responsible for anti-phospholipid syndrome, reactive arthritis, uveitis, and carpal tunnel syndrome.^{2,18,19} Antiganglioside antibodies were detected in a 69-year-old white man with neurological complications of leptospirosis presenting with meningo-myeloencephalopolyneuritis and nephrotic syndrome.²⁰

Treatment of severe leptospirosis patients is supportive management and use of appropriate antibiotics. Corticosteroid therapy is controversial since most cases of acute leptospirosis resolve spontaneously. However, thrombocytopenia and autoimmune hemolytic anemia in a case of pediatric leptospiral pneumonia were successfully treated with pulse doses of methylprednisolone at 30 mg/kg every 8 hours.²¹ As a result of the limited number of published randomized clinical trials, there is insufficient evidence to guide practice. Doxycycline, ampicillin and amoxicillin are recommended for mild disease, whereas penicillin G and ceftriaxone are indicated for acute severe leptospirosis.² The fluoroquinolones have *in vitro* activity against *Leptospira* spp. and may be effective therapy in animal studies, but ofloxacin was unable to clear bacteria from blood or kidneys in a hamster model.²² Plasma exchange has also been reported as adjunctive therapy for patients with severe Weil's disease who have not shown rapid clinical response to conventional treatment.²³

Leptospirosis was previously reported as unilateral pneumonia, pleural effusion, and anti-I cold hemagglutinin antibodies in a previously healthy 5-year-old Chamorro girl.²¹ Although cold hemagglutinin disease may be associated with infections due to Epstein–Barr virus, cytomegalovirus, and mumps virus, anti-I hemagglutinin is most commonly associated with *M. pneumoniae*. The child was treated accordingly, but did not improve. Exposure history and laboratory data suggested leptospirosis, and the child completely recovered with 10 days of penicillin and erythromycin. Autoimmune hemolysis after the phase of leptospiremia and concurrent hemolytic anemia suggests that cold hemagglutinin antibody may play a significant role in the genesis of acquired hemolytic anemia in sheep.²⁴ The complete *L. interrogans* strain Lai genome resembles *Mycoplasma genitalium* in terms of the number of proteins with structural similarity to the eukaryal and archaeal proteins that it encodes.²⁵ Although co-infection with leptospirosis and *Mycoplasma* is possible, antigenic mimicry may play a role in biological false-positive reactions.

Leptospirosis has been recognized as an acute infection in the literature²; however, few of its chronic manifestations have been described.^{9,19} We have observed that leptospirosis may significantly contribute to comorbidity. Overwhelming infections can be caused by leptospirosis in patients with an obvious exposure history and prior blunt trauma or recent bleeding as a triggering event.⁹ Neuroleptospirosis should be considered in the differential diagnosis of neurological involvement associated with hepatorenal dysfunction. This case serves to remind clinicians that peripheral nerve palsy is a potential clinical feature of leptospirosis.

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