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Case report

Travel-related leptospirosis in Japan: A report on a series of five imported cases diagnosed at the National Center for Global Health and Medicine

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ABSTRACT

Leptospirosis is one of the most common travel-related infections. We report 5 cases of travel-related leptospirosis who presented at our clinic between January 2008 and December 2013. Patients were included in the study if they presented with a clinical profile that was compatible with the disease within 21 days of their return from traveling, which were laboratory-diagnosed as leptospirosis by blood culture, rise in antibody titers in paired sera using the microscopic agglutination test (MAT), and/or DNA detection using *flaB*-nested PCR. Five leptospirosis cases were evaluated, all of which contracted the disease after exposure to fresh water in Southeast Asian countries. All of the cases had fevers, headaches, conjunctival injections, and relative bradycardia. The pertinent laboratory findings included elevated C-reactive protein levels, elevated creatinine levels, and sterile pyuria. All 5 cases had serum MAT titers that increased by $\geq$ 4 times in the interval between specimens taken during the acute phase and those taken during the convalescence phase, and leptospiral DNA was detected in plasma and/or urine specimens in 4 cases. *Leptospira interrogans* was isolated from one patient's blood sample. Patients were treated with penicillin G, minocycline, or doxycycline. One case was cured without antibiotics. A diagnosis of leptospirosis should be considered for febrile travelers who return from Southeast Asian countries to Japan after being exposed to freshwater while traveling.

1. Introduction

Leptospirosis, a zoonotic infection caused by the pathogenic spirochetes of the genus *Leptospira*, is endemic in tropical regions. Human infection can occur either through direct contact with infected animals or through contact with water or soil contaminated by the urine of infected animals [1]. About 25 cases of leptospirosis are reported every year in Japan [2].

Leptospirosis is one of the most important differential diagnoses associated with febrile illness in returned travelers. The clinical manifestations of leptospirosis are non-specific, are similar to those associated with dengue fever, malaria, or typhoid fever, and may include fever accompanied by headaches, arthralgia, and myalgia. Outbreaks of leptospirosis are occasionally reported in tropical regions, especially in relation to flooding [3] or watersports [4]. According to the national surveillance data, only 19 cases of imported leptospirosis have been reported since November 2003 [2]. Consequently, little clinical information about imported leptospirosis cases is available in Japan.

The aim of this case report is to better characterize the epidemiologic, clinical, and laboratory profiles of patients diagnosed with travel-related leptospirosis in Japan.

2. Case report

There were 5 cases of travel-related leptospirosis who were diagnosed between January 2008 and December 2013 at the Disease Control and Prevention Center, National Center for Global Health and Medicine (NCGM), Tokyo, Japan. Laboratory diagnosis of leptospirosis was made by blood culture, DNA detection and/or

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antibody detection. To isolate leptospires, one hundred microliter of blood were inoculated into 4 ml of liquid Korthof's medium containing 10% rabbit serum, and cultivated at 30 °C. DNA detection was performed with *flaB*-nested PCR from plasma, serum and/or urine followed by direct nucleotide sequencing of the amplicons [5]. The microscopic agglutination test (MAT) was performed for detecting anti-*Leptospira* antibodies in patient serum samples using a battery of previously described reference strains [6]. At least a 4 fold increase in antibody titers between acute and convalescent serum samples was judged as positive.

2.1. Case 1

The patient was a 48-year-old Japanese man who had undertaken river and jungle surveys on the island of Borneo in Malaysia from February 16 to March 12, 2010. On March 10, 2010, he had a fever, headaches, and myalgia. On March 13, 2010, he attended a clinic at the NCGM. He had a medical history of malaria caused by *Plasmodium vivax* infection and enteric fever. On examination, he had a blood pressure of 133/80 mmHg, a temperature of 38.6 °C, and a pulse rate of 88 beats/min. Findings from his physical examination were normal, except for bilateral conjunctival injection. His laboratory tests revealed leukocytosis, an elevated serum creatinine level, pyuria, hematuria, and proteinuria. influenza, dengue fever, including those to detect the viral antigen, NS1, and the virus-specific antibody types IgM and IgG, the malaria rapid diagnosis test, Giemsa staining, and 2 sets of blood cultures were negative. On March 16, 2010, *Leptospira* DNA was detected in the plasma, serum, and urine by PCR. We diagnosed leptospirosis and began administering intravenous penicillin G (PCG). A high-grade fever was observed 12 h after the first administration of PCG, which was considered to be associated with the Jarisch–Herxheimer reaction. His fever and symptoms subsided within approximately 1 day. A 7-days course of antibiotics was completed. The inoculation of blood into Korthof's medium led to the isolation of *Leptospira interrogans*. MAT revealed a >4-fold increase in antibody titers against several strains in paired serum samples, and the highest titer was observed against a strain of *L. interrogans* serovar Autumnalis.

2.2. Case 2

Case 2 was a previously healthy 43-year-old Japanese man who had visited Chiang Mai, Thailand from September 28 to October 8, 2011 for a tour of the ethnic Karens. He had bathed in rivers during the tour. On October 11, 2011, he had a fever, headaches, and arthralgia. On October 14, 2011, he attended a clinic at the NCGM. An examination revealed normal findings except for a fever of 39.4 °C and a pulse rate of 114 beats/min, and bilateral conjunctival injection. Laboratory tests revealed hyperbilirubinemia, an elevated serum creatinine level, thrombocytopenia, and proteinuria. Tests for influenza, dengue fever, including those to detect the viral antigen, NS1, and the virus-specific antibody types IgM and IgG, the malaria rapid diagnosis test, Giemsa staining, and 2 sets of blood cultures were negative. Following hospitalization, intravenous minocycline was initiated, because leptospirosis or rickettsiosis was suspected. His fever and symptoms subsided within approximately 3 days. The intravenous minocycline was switched to oral doxycycline. On October 19, 2011, PCR detected *Leptospira*-specific DNA in serum and urine samples. He completed a 7-day course of antibiotic treatment. MAT revealed a >4-fold increase in antibody titers against several strains in paired serum samples, and the highest titer was observed against a strain of *L. interrogans* serovar Hebdomadis.

2.3. Case 3

Case 3 was a previously healthy 19-year-old Japanese man who had visited the island of Borneo in Malaysia from November 1 to November 9, 2012 as a volunteer. During his travels, he took a lustral bath during a religious ceremony. On November 12, 2012, he had a fever, headaches, cough, and nausea, but the symptoms subsided spontaneously within 1 day. On November 16, 2012, the fever, headaches, arthralgia, and cough reemerged, and on November 18, 2012, he attended a clinic at the NCGM. At his first presentation, he did not have a fever. A physical examination revealed normal findings except for bilateral conjunctival injection (Fig. 1). Laboratory tests revealed leukocytosis, elevated serum creatinine and creatine kinase levels, proteinuria, and pyuria. Tests for dengue fever, including those to detect the viral antigen, NS1, and the virus-specific antibody types IgM and IgG, the malaria and leptospirosis rapid diagnosis tests, Giemsa staining, and 2 sets of blood cultures were negative. Following hospitalization, his body temperature rose to 39.4 °C. Oral doxycycline and intravenous ceftriaxone were initiated, because we suspected either leptospirosis or typhoid fever. His fever and symptoms subsided within approximately 2 days. On November 26, 2012, PCR detected *Leptospira*-specific DNA in his plasma, and we diagnosed leptospirosis. Intravenous ceftriaxone was discontinued and he completed a 7-day course of doxycycline treatment. MAT revealed a >4-fold increase in antibody titers against several strains in paired serum samples, and the highest titer was observed against strains of leptospiral serovars Batavaie, Hebdomadis, and Poi.

2.4. Case 4

Case 4 was a previously healthy 21-year-old Japanese man who had visited Vietnam, Thailand, Malaysia, Cambodia, Laos, and Brunei from August 1 to September 24, 2013 on a backpacking trip. On September 10, 2013, he had trekked and had immersed himself in a river at Chiang Mai, Thailand. On September 21, 2013, he had a fever and headaches. On September 24, 2013, he attended a clinic at the NCGM. An examination showed he had a high-grade fever, with a body temperature of 39.1 °C and a pulse rate of 91 beats/min. He also had bilateral conjunctival injection. Laboratory tests revealed thrombocytopenia, and elevated levels of liver enzymes and serum creatinine. Tests for dengue fever, including those to detect the viral antigen, NS1, and the virus-specific antibody types IgM and IgG, the malaria rapid diagnosis test, and Giemsa staining were negative. Since his general condition was good, we decided to manage him in the outpatient department without antibiotics. His fever and

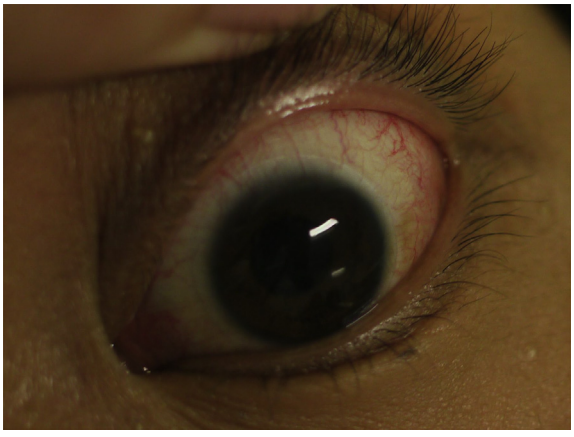

Fig. 1. Conjunctival injection in Case 3.