Short Communication

Leptospirosis Cases in the Tokyo Metropolitan Area, Japan

Yoshikazu Mutoh^{1*}, Nobuo Koizumi², Eriko Morino¹, Kayoko Hayakawa¹, Yasuyuki Kato¹,
and Norio Ohmagari¹

¹Disease Control and Prevention Center, National Center for Global Health and Medicine, Tokyo; and

²Department of Bacteriology I, National Institute of Infectious Diseases, Tokyo, Japan

SUMMARY: In Japan, 20–50 cases of leptospirosis are reported annually, typically involving farmers or returnees from tropical areas. Here, we report on 5 indigenous leptospirosis cases that occurred in the Tokyo urban area. All patients were men (mean age, 66.4 ± 4.6 [SD] years) and presented with clinical features that included high fever, acute kidney injury, and jaundice. Three patients presented with pulmonary infiltration and ground-glass opacity on admission. Two of the 5 patients were intubated and underwent continuous hemodiafiltration. The mean length of hospitalization was 38.0 ± 17.0 days, and all patients were treated successfully with antibiotics. Notably, all patients had a history of exposure to rats prior to becoming symptomatic, suggesting that exposure to rats is a risk factor for urban leptospirosis. Although rare, even in metropolitan areas, leptospirosis should be considered by physicians when patients present with severe sepsis, acute kidney injury, and a history of exposure to rats.

Leptospirosis is a well-known zoonotic disease. Severe leptospirosis is referred to as “Weil’s disease”, after Adolf Weil who first described the disease in 1886 (1). In 1914, Inada et al. detected spirochetes in the blood of patients with Weil’s disease (2). The pathogens, *Leptospira* spp., are harbored in the kidneys of rodents, pigs, or cattle, and cause disease in humans. At risk are men, individuals exposed to soil and water contaminated with the urine of a carrier animal, individuals participating in outdoor leisure activities, agricultural and construction-site laborers, or individuals exposed to sewage treatment systems (3–5). Outbreaks often occur after heavy rainfall, during floods, or following adventure races (6).

In Japan, the number of deaths from leptospirosis ranged from 50–250 annually until the 1970s and often occurred during the summer or fall. Therefore, the illness was called “aki-yami” (meaning “fall-disease”). The incidence of leptospirosis has decreased rapidly with industrialization and a decline in the number of agricultural workers. Leptospirosis was designated as a notifiable infectious disease in 2003, and 20–50 cases are now reported annually in Japan. One-third of these cases are associated with outdoor sports or recreational exposure to freshwater environments in Okinawa, the southernmost subtropical prefecture of Japan. Tokyo, Japan’s capital city, has the second largest number of leptospirosis cases in Japan.

There have been increasing reports of leptospirosis in urban areas and slums in other countries (7). Moreover, urban leptospirosis is an occupational disease

closely associated with an increasing number of rat infestations in Europe (8) and is becoming an urban health problem. Hence, this study sought to investigate the characteristics, settings, risk factors, and differences between the 5 urban leptospirosis cases compared with previously reported travel-related cases.

Our hospital, the National Center for Global Health and Medicine, is a 781-bed acute care hospital in Shinjuku, the most densely populated area in Tokyo. From 2006 to 2015, 5 cases of leptospirosis, possibly infected in Tokyo, presented at our hospital (Table 1). Anti-leptospiral antibodies were detected by microscopic agglutination tests (MATs) in all patients (9): 3 cases had antibody titers that were highest against serogroup Icterohaemorrhagiae, 1 against Autumnalis, and the other against Javanica. In Patient 2, although the paired serum samples did not show a 4-fold rise in titer, the titer in the acute phase was already high enough to indicate acute *Leptospira* infection. In addition, the patient had symptoms compatible with a diagnosis of leptospirosis. Leptospiral DNA was detected in 2 patients by *flaB*-nested PCR (9). One of the nucleotide sequences (accession number LC219370), which was detected in a serum specimen from Patient 3, was identical to that of *Leptospira interrogans* serogroup Icterohaemorrhagiae isolated from rats captured in Tokyo. The nucleotide sequences detected from serum and urine specimens (LC219371 and LC219372) in Patient 4 were identical to each other but differed from the sequence in Patient 3 in 2 nucleotides.

All patients were men with a mean age of $66.4 (\pm 4.6)$ years) and lived in Tokyo. All patients developed symptoms within 7 days prior to admission and presented with shock on arrival. Patients 1 and 5 had a history of tuberculosis, and Patient 5 was receiving treatment for HIV. Patient 2 had a physical disability due to cerebral palsy. None of the patients had been overseas or had been exposed to heavy rain, fresh water, or flood. However, in all cases, rats were present in their living or working environments. Patients 1 and 3 worked in the

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*Corresponding author: Mailing address: Disease Control and Prevention Center, National Center for Global Health and Medicine, 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan. Tel: +81-3-3202-7181, Fax: +81-3-3207-1038, E-mail: tsu_ka_sa31@yahoo.co.jp

Table 1. Characteristics of the 5 cases of indigenous leptospirosis in Tokyo, Japan

No.	Diagnosis date	Citizenship	Age (yr)	Sex	Occupation	Comorbid illness	Clinical symptom	Conjunctival suffusion	Eruption in the pretibial region	MAT (serogroup)		PCR
										Acute	Conv.	
1	Nov. 2005	JPN	65	M	butcher	HTN	fever, fatigue, runny nose, myalgia, rash	+	+	Icterohaemorrhagiae < 20	Icterohaemorrhagiae 160	NT
2	Aug. 2006	JPN	62	M	unemployee	cerebral palsy	fever, diarrhea, vomiting, cons loss, appetite loss, jaundice	—	—	Icterohaemorrhagiae 160	Icterohaemorrhagiae 160	NT
3	Jan. 2012	JPN	64	M	delicatessen	HTN Paf	fever, myalgia, arthralgia, jaundice	+	+	Autumnalis < 20	Autumnalis 640	blood
4	Dec. 2014	JPN	74	M	unemployee	none	fever, cons loss, weakness, rash, myalgia	—	+	Javanica < 50	Javanica 1,600	blood urine
5	Feb. 2015	JPN	67	M	cleaner	HIV miliary tuberculosis	fever, cons loss, fatigue, dyspnea	unknown	unknown	Icterohaemorrhagiae < 50	Icterohaemorrhagiae 1,600	NT

MAT, microscopic agglutination test; PCR, polymerase chain reaction; HTN, hypertension; NT, not tested; cons loss, loss of consciousness; Paf, paroxysmal atrial fibrillation.

food industry, and Patient 2 lived in a house full of garbage. Many rats were seen in their workplaces or homes and the patients' bare hands or feet were often in contact with rat urine. Patient 4 was a homeless man and lived near a sewer where rats and rat urine were often seen. Patient 5 was frequently exposed to rats in his backyard. Two of the 5 patients required intubation because they were unconscious and had severe respiratory failure on admission. Three of the 5 patients underwent renal replacement therapy.

Patient 1 was suspected of having a hematological disorder on admission because he presented with thrombotic thrombocytopenic purpura (TTP)-like symptoms. It has been reported that leptospirosis can present as TTP-like illness (10) and thus should be considered in the differential diagnosis of patients with TTP-like symptoms, even in indigenous cases. Three of our 5 patients were found to have pulmonary infiltration on chest computed tomography (CT) in the early phase. Ground-glass opacity (GGO) was seen mainly in the basal lung regions in Patients 1 and 4. There was consolidation in the dorsal segment of the left lung in Patient 5, and he required intubation. Gulati et al. reported pulmonary involvement in 20–70% of patients in the immune phase with pulmonary radiographic alterations varying from 11% to 67% (11), and GGO revealed by CT was due to airspace hemorrhage. All patients in this study survived without residual symptoms, and the mean length of hospitalization was 38.0 days ($\pm$ 17.0 days). Ceftriaxone was used to treat 3 of the 5 patients and the remaining patients were treated with carbapenem.

Our five cases occurred mainly during winter, although most leptospirosis cases are reported during summer in Okinawa Prefecture because of exposure during freshwater recreational activities. Nevertheless, in urban areas, leptospirosis has no relationship with these types of activities and so can occur during any season. Desai

et al. reported the occurrence of outbreaks of leptospirosis even in winter (12).

We compared our 5 indigenous cases of leptospirosis with travel-related cases that we previously reported, which were associated with freshwater recreational activities (13). Although all patients among both the indigenous and overseas travel-related cases were men and required hospital treatment, the indigenous patients were older and presented with more severe symptoms of renal and liver dysfunction than the travel-related cases (Table 2). Three of the 5 indigenous patients were presumed to be infected with serogroup Icterohaemorrhagiae, but no antibodies against this serogroup were detected in the travel-related cases. Virulence properties are thought to differ among *Leptospira* serovars or serogroups, and serogroup Icterohaemorrhagiae is particularly associated with severe disease (14). Therefore, older age and the infecting serogroup seem to be risk factors for severe urban leptospirosis. In addition, our cases had a history of contact with rats and a particular nucleotide sequence detected from one of our patients was identical to that isolated from rats, strongly suggesting that leptospirosis may be caused by wild rats in urban areas of Tokyo. It has been reported that 17.3% of brown rats in Tokyo carry *Leptospira* in their kidneys (15). Thus, the number of leptospirosis cases in urban areas might be greater than would be expected by physicians.

In conclusion, we have described 5 cases of indigenous leptospirosis in urban areas of Tokyo. Despite the extreme rarity of the disease and severity of the symptoms, we successfully diagnosed and treated all cases promptly. It is essential for physicians to suspect leptospirosis when patients present with fever of unknown origin, elevated liver enzymes, acute kidney injury, and a potential history of exposure to rats, even if they reside in urban areas. Further studies on the epidemiology and risk factors in urban areas are required, as well as further

Table 2. Laboratory data and outcome of indigenous cases

No.	Intubation	CHDF	WBC (/ μ L)	Platelet ($\times 10^4$ / μ L)	Total bilirubin (mg/dL)	Creatinine (mg/dL)	CK (IU/L)	AST/ALT (IU/L)	Duration of stay (days)	Outcome
1	no	no	15,100	1.1	10.3	6.6	287	51/48	47	survive
2	yes	yes	13,300	2.3	11.7	6.5	4,948	171/63	64	survive
3	no	no	15,100	4.4	10.6	3.4	4,092	214/142	24	survive
4	no	no	15,030	3.9	2.8	5.1	9,048	272/153	16	survive
5	yes	yes	19,200	2.9	12.6	8.3	2,906	92/137	39	survive

CHDF, continuous hemodiafiltration; WBC, white blood cell; CK, creatinine kinase; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

training for physicians on the diagnosis of leptospirosis.

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Conflict of interest None to declare.

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