Leptospirosis cases in the Tokyo Metropolitan area, Japan

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Summary

In Japan, 20-50 cases of leptospirosis are reported annually, typically involving farmers or returnees from tropical areas. Here, we report five indigenous leptospirosis cases that occurred in the Tokyo urban area. All cases were male (mean age 65.8 ± 4.7 years) and presented with clinical features including high fever, acute kidney injury, and jaundice. Three cases presented with pulmonary infiltration and ground glass opacity on admission. Two of the five patients were intubated and underwent continuous hemodiafiltration. The mean length of hospitalization was 38 ± 17.0 days, and all patients were treated 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 participate 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 in 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 industrial development 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 our five 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 population-dense area in Tokyo. From 2006 to 2015, five cases of leptospirosis, possibly infected in Tokyo, presented at our hospital (Table 1). Anti-leptospiral antibodies were detected in all patients by microscopic agglutination tests [9]: three cases had antibody titers highest against serogroup Icterohemorrhagiae, one 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 and the patient had symptoms compatible with a diagnosis of leptospirosis. Leptospiral DNA was detected in two 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 *L. interrogans* serogroup Icterohemorrhagiae isolated from rats captured in Tokyo. The nucleotide sequences detected from serum and urine specimens in Patient 4 (LC219371 and LC219372) were identical to each other but differed from the above sequence by 2 nucleotides.

All patients were male with a mean age of 65.0 (± 4.7 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 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 five patients required intubation because they were unconscious and had severe respiratory failure on admission. Three of the five patients underwent renal replacement therapy.

Patient 1 was suspected to have a hematological disorder at 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 five 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 days (± 17.0 days). Ceftriaxone was used in three of the five 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 five 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 male 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 five indigenous patients were presumed to be infected with serogroup Icterohemorrhagiae, 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 Icterohemorrhagiae is particularly associated with severe disease [14]. Therefore, older age and the infecting serogroups 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 five 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 renal failure, 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 training for physicians on the diagnosis of leptospirosis.

Acknowledgments

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Conflict of interest

None to declare


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

<table>
<thead>
<tr>
<th>No.</th>
<th>diagnosis date</th>
<th>citizenship</th>
<th>age (years)</th>
<th>sex</th>
<th>occupation</th>
<th>comorbid illness</th>
<th>clinical symptom</th>
<th>conjunctival suffusion</th>
<th>eruption in the pretibial region</th>
<th>MAT(^1) (serogroup)</th>
<th>PCR(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Nov 2005</td>
<td>JPN</td>
<td>65</td>
<td>M</td>
<td>butcher</td>
<td>hypertension</td>
<td>fever, fatigue, runny nose, myalgia, rash</td>
<td>+</td>
<td>+</td>
<td>Icterohaemorrhagiae &lt;20</td>
<td>Icterohaemorrhagiae 160</td>
</tr>
<tr>
<td>2</td>
<td>Aug 2006</td>
<td>JPN</td>
<td>62</td>
<td>M</td>
<td>unemployee</td>
<td>Cerebral palsy</td>
<td>fever, diarrhea, vomiting, cons loss, appetite loss, jaundice</td>
<td>-</td>
<td>-</td>
<td>Icterohaemorrhagiae 160</td>
<td>Icterohaemorrhagiae 160</td>
</tr>
<tr>
<td>3</td>
<td>Jan 2012</td>
<td>JPN</td>
<td>64</td>
<td>M</td>
<td>delicatessen</td>
<td>HTN(^4), Paf(^5)</td>
<td>fever, myalgia, arthralgia, jaundice</td>
<td>+</td>
<td>+</td>
<td>Autumnalis &lt;20</td>
<td>Autumnalis 640</td>
</tr>
<tr>
<td>4</td>
<td>Dec 2014</td>
<td>JPN</td>
<td>74</td>
<td>M</td>
<td>homeless</td>
<td>none</td>
<td>fever, cons loss, weakness, rash, myalgia</td>
<td>-</td>
<td>+</td>
<td>Javanica &lt;50</td>
<td>Javanica 1600</td>
</tr>
<tr>
<td>5</td>
<td>Feb 2015</td>
<td>JPN</td>
<td>67</td>
<td>M</td>
<td>cleaner</td>
<td>HIV miliary tuberculous</td>
<td>fever, cons loss, fatigue, dyspnea</td>
<td>unknown</td>
<td>unknown</td>
<td>Icterohaemorrhagiae &lt;50</td>
<td>Icterohaemorrhagiae 160</td>
</tr>
</tbody>
</table>

1) MAT: Microscopic agglutination test \hspace{1cm} 2) PCR: Polymerase chain reaction \hspace{1cm} 3) NT: Not tested
4) HTN: Hypertension \hspace{1cm} 5) Paf: Paroxysmal atrial fibrillation
Table 2. Laboratory data and outcome of indigenous cases.

<table>
<thead>
<tr>
<th>No.</th>
<th>intubation</th>
<th>CHDF (^1)</th>
<th>leukocytosis (µ/L)</th>
<th>thrombocytopenia (×10^4 µ/L)</th>
<th>hyperbilirubinemia (mg/dl)</th>
<th>creatinine (mg/dl)</th>
<th>CK (^2) (IU/L)</th>
<th>AST (^3)/ALT (^4) (IU/L)</th>
<th>duration of stay (days)</th>
<th>outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>no</td>
<td>no</td>
<td>15,100</td>
<td>1.1</td>
<td>10.3</td>
<td>6.6</td>
<td>287</td>
<td>51/48</td>
<td>47</td>
<td>survive</td>
</tr>
<tr>
<td>2</td>
<td>yes</td>
<td>yes</td>
<td>13,300</td>
<td>2.3</td>
<td>11.7</td>
<td>6.5</td>
<td>4948</td>
<td>171/63</td>
<td>64</td>
<td>survive</td>
</tr>
<tr>
<td>3</td>
<td>no</td>
<td>no</td>
<td>15,100</td>
<td>4.4</td>
<td>10.6</td>
<td>3.4</td>
<td>4092</td>
<td>214/142</td>
<td>24</td>
<td>survive</td>
</tr>
<tr>
<td>4</td>
<td>no</td>
<td>no</td>
<td>15,030</td>
<td>3.9</td>
<td>2.8</td>
<td>5.1</td>
<td>9048</td>
<td>272/153</td>
<td>16</td>
<td>survive</td>
</tr>
<tr>
<td>5</td>
<td>yes</td>
<td>yes</td>
<td>19,200</td>
<td>2.9</td>
<td>12.6</td>
<td>8.3</td>
<td>2906</td>
<td>92/137</td>
<td>39</td>
<td>survive</td>
</tr>
</tbody>
</table>

1) CHDF: Continuous hemodiafiltration  
2) CK: Creatinine kinase  
3) AST: Aspartate transaminase  
4) ALT: Alanine aminotransferase