CASE REPORT

Severe leptospirosis in a patient with positive serological test for spotted fever rickettsiosis

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SUMMARY

Here, we report a case of a 64-year-old man with severe leptospirosis infected in an area in Japan that is non-endemic to leptospirosis. Initially, findings of high-grade fever, mild generalised arthralgia, rashes on the trunk, mild thrombocytopenia, elevated liver enzymes and renal dysfunction led to the suspicion of rickettsiosis, which was an endemic infectious disease in the area. Subsequently, leptospirosis was also considered after carefully reviewing patient history, which revealed that he may have been exposed to mice urine. Finally, leptospirosis was diagnosed after the serum indicated a positive PCR for leptospirosis. Furthermore, due to serum antibody positivity for *Rickettsia japonica*, false-positivity or coinfection of spotted fever rickettsiosis was suspected. Despite the delayed diagnosis, the patient recovered with antibiotic treatment. Thus, to prevent diagnostic errors, leptospirosis should be potentially considered with high suspicion in patients with acute undifferentiated fever, even in non-endemic areas of leptospirosis.

BACKGROUND

Leptospirosis is a bacterial zoonotic disease and can be potentially fatal in severe cases.¹ A prompt and accurate diagnosis of leptospirosis is crucial to reduce mortality in patients with a severe infection. Additionally, an inaccurate or delayed diagnosis of leptospirosis can easily occur in specific cases such as in those originating in endemic or epidemic area of other infectious diseases and non-endemic areas of leptospirosis.^{2–4} Here, we report the case of a patient with a delayed diagnosis of severe leptospirosis and a positive serological test for spotted fever rickettsiosis. The case originated in an area in Japan where leptospirosis was not endemic but rickettsiosis was. Written consent was obtained from the patient.

CASE PRESENTATION

A 64-year-old man presented with a 1-day history of high-grade fever, fatigue and mild generalised arthralgia in late summer. He reported no cough, rhinorrhoea, sore throat, myalgia, headache, dyspnoea, abdominal pain, nausea or diarrhoea. The patient's medical history included hypertension, dyslipidaemia and gastro-oesophageal reflux disease. He regularly consumed the following medications: valsartan, amlodipine and esomeprazole. The patient was a part-time farmer and lived in an area that was endemic for rickettsiosis. Physical

examination revealed that his body temperature was 37.5°C, blood pressure was 87/53 mm Hg, pulse rate was 98 beats per minute, respiratory rate was 14 breaths per minute and oxygen saturation at ambient air was 97%. His conjunctiva was mildly icteric but did not indicate suffusion and showed supple neck. Heart and lung examinations were normal. Abdominal distension, tenderness or hepatosplenomegaly were absent. Skin examination revealed no rash, either petechial or eschar. Remaining examinations were unremarkable. Laboratory tests were performed on the hospitalisation day 1 and indicated neutrophil dominant mild leucocytosis (white blood cell count, $8.64 \times 10^9/L$; neutrophil count, 89.2%); mild thrombocytopenia (platelet count $112 \times 10^9/L$); elevated levels of serum aspartate aminotransferase (88 U/L), alanine aminotransferase (109 U/L), total bilirubin (2.9 mg/dL), creatinine (1.29 mg/dL) and C-reactive protein (18.65 mg/dL). Neither hepatitis B surface antigen nor hepatitis C antibody was positive. Urinalysis detected a moderate proteinuria. Chest and abdominal CT without contrast revealed no pulmonary infiltration, hepatosplenomegaly, lymphadenopathy or other abnormalities. Blood culture performed on day one demonstrated no bacterial growth. Initially, the patient was suspected with systemic viral infection, particularly due to enterovirus (eg, echovirus and coxsackievirus). Although other viral infections, including hepatitis A, hepatitis E, dengue, Epstein-Barr virus and cytomegalovirus, seemed retrospectively possible, we did not consider them in the differential diagnosis. Therefore, we did not perform any serological tests for those infections, and the patient was treated with intravenous hydration without antibiotics. However, his condition did not improve, and on day 3, he developed nausea, mild headache and slight erythematous macules on the trunk and proximal portion of the extremities. In addition to viral infection, he was also suspected with bacterial infection, particularly rickettsiosis, which was endemic in the area he lived in. Cholangitis and hepatic abscess were also considered in the differential diagnosis although the possibility was considered low. Therefore, he was intravenously administered piperacillin/tazobactam and minocycline. Several hours after initiating the antimicrobial therapy, his body temperature elevated to 40°C accompanied by chills. On day 5, his body temperature gradually normalised. However, a progression of fatigue, jaundice (total bilirubin level increased to 4.6 mg/dL), thrombocytopenia (platelet count decreased to $33\,000/\mu L$) and renal insufficiency

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(creatinine level increased to 5.49 mg/dL) were observed. Similarly, the levels of serum alkaline phosphatase (559 U/L) and creatinine phosphokinase (771 U/L) were elevated. Importantly, a subsequent and more accurate history taking revealed that the patient came into contact with wild mice and was exposed to water that may have been contaminated with mice urine. Consequently, leptospirosis was suspected as a possible diagnosis, along with rickettsiosis as an alternate diagnosis. Thus, the antibiotic spectrum was narrowed by replacing piperacillin/tazobactam with ceftriaxone, and minocycline was continued. On day 19, serum PCR for leptospirosis was reported to be positive. In addition, antibodies for *Leptospira borgpetersenii* serovar Poi, *Leptospira* serovar autumnalis and *Leptospira interrogans* serovar kremastosis showed at least a fourfold increase in paired serum samples (<1:50 at day 1 and 1:200 at day 12). However, the patient indicated serum antibody positivity for *Rickettsia japonica* (<1:40 at day 1 and 1:160 at day 16). Therefore, a final diagnosis of leptospirosis with coinfection of spotted fever rickettsiosis or false positivity for rickettsiosis was established.

OUTCOME AND FOLLOW-UP

Following completion of the antibiotic therapy, the patient's symptoms resolved, and his laboratory abnormalities, except for renal function (serum creatinine level, 1.98 mg/dL at day 22), normalised.

DISCUSSION

Here, we report a case of severe leptospirosis in a patient who lived in an area non-endemic for this disease, accompanied by a possible coinfection of rickettsiosis. The patient made a near-complete recovery, except for the renal abnormality. However, this diagnosis of leptospirosis was delayed. Initially, we considered rickettsiosis as differential diagnosis, whereas leptospirosis was excluded. This case suggests that a diagnostic delay or misdiagnosis of leptospirosis is possible, especially in cases originating in non-endemic areas of leptospirosis. We believe this may be due to mainly two reasons.

First, diagnostic delay may occur in cases where the disease originates in non-endemic areas of leptospirosis. Leptospirosis is an uncommon disease in Japan. Reportedly, the annual incidence of leptospirosis is very low (0.01–0.03 per 100 000 people).⁵ Additionally, for leptospirosis cases reported in Japan, the mean duration of disease was approximately 6 days from symptom onset to treatment initiation.⁴ Specifically, leptospirosis was not included in the initial differential diagnosis in our patient because this case occurred in Nagano, a prefecture of Japan with no reported case of leptospirosis between 2007 and 2016.⁶ Although Nagano lies in the Kanto–Koshinetsu region wherein 44 of 258 domestic cases of leptospirosis (17% of total domestic cases) occurred during the same time, it was far from the Kyushu–Okinawa region, which is the most endemic area of leptospirosis in Japan (175 cases, 68%).⁶ Importantly, the final diagnosis could have been missed or delayed if a more accurate history was not procured. Detailed history-taking helped determine that the patient was recently in contact with wild mice and had been exposed to water, which may have been contaminated with mice urine. This case highlights the importance of obtaining a medical history additionally focused on patients' exposure to wild animals, especially in cases with an acute undifferentiated fever, to avoid diagnostic errors.

Second, a wrong or delayed diagnosis of leptospirosis can also occur in cases originating in areas endemic for other infectious diseases which may be clinically similar to leptospirosis.

For example, under detection or misdiagnosis of leptospirosis in patients living in endemic areas of dengue were reported in several countries, despite the areas also being endemic for leptospirosis.^{2 7 8} With respect to diagnostic delay, a retrospective study from Brazil reported that during the epidemic season of dengue and leptospirosis, an initial misdiagnosis as dengue was associated with a median delay of 5 days between first health service visit and arrival at the infectious disease reference hospital in patients with leptospirosis.³ As to our patient, leptospirosis could not have been detected if relevant diagnostic tests were not conducted for it. This was because the patient's symptoms were consistent with rickettsiosis, an infectious disease clinically similar to leptospirosis and dengue,⁹ and because the patient lived in a non-endemic area for leptospirosis. Specifically, increased serum antibodies for *R. japonica* could have been considered as an evidence of true infection for rickettsiosis. Thus, careful monitoring with a suspicion of leptospirosis in patients with undifferentiated fever is the only way to avoid the missed diagnosis of leptospirosis in areas with high prevalence of dengue or rickettsiosis.

Coinfection of leptospirosis and rickettsiosis was another possibility in the present case. A study from Thailand reported a coinfection of scrub typhus and leptospirosis in up to 40% of patients with leptospirosis.¹⁰ Similarly, coinfection of leptospirosis and scrub typhus was also observed in several patients in Taiwan.¹¹ However, these reports were based on only serological tests. An independent study reported that of the cases diagnosed with coinfection of leptospirosis and scrub typhus based on serological tests, only 6% were confirmed as true coinfection using PCR for the 16S ribosomal RNA genes.¹² Therefore, positive serological tests for scrub typhus in patients with leptospirosis could be due to a false-positivity linked to several mechanisms including cross-reactivity.¹² Moreover, until now, there are no reports of leptospirosis and spotted fever rickettsiosis coinfection. Therefore, in the present case the positive serological tests for *R. japonica* seemed to be false positive. However, the chance of a true coinfection could not be ruled out.

A delayed or missed diagnosis of leptospirosis can occur in cases originating in non-endemic areas of leptospirosis, due to its low prevalence as opposed to the high prevalence of other infectious diseases that are clinically similar to leptospirosis. To prevent diagnostic errors, careful monitoring with high suspicion of leptospirosis in patients with acute undifferentiated fever is essential, even in non-endemic areas of leptospirosis.

Learning points

- ▶ A differential diagnosis for leptospirosis should be considered in patients with acute undifferentiated fever, even in non-endemic areas of leptospirosis.
- ▶ A missed or delayed diagnosis of leptospirosis may occur in cases originating areas of endemic for other infectious diseases.
- ▶ Coinfection of leptospirosis and rickettsiosis may exist. Moreover, the results of serological tests should be interpreted with caution owing to the possibility of false-positivity.

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