Severe Murine Typhus With Shock and Acute Respiratory Failure in a Japanese Traveler After Returning From Thailand

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We treated a case of severe murine typhus in a Japanese traveler after returning from Thailand. Although the disease is typically self-limited or mild, the patient showed shock and multiple organ failure including acute respiratory distress syndrome. Then the patient fully recovered following intensive care and administration of antirickettsial medicines.

Murine typhus, a type of rickettsial infection caused by *Rickettsia typhi*, is found worldwide, particularly in North and South America, Southeast Asia, Africa, Australia, and southern European countries. Cases where international travelers acquired murine typhus after traveling to endemic areas have occasionally been reported. Since murine typhus manifests itself by various nonspecific symptoms, such as fever, headache, rash, myalgia, arthralgia, diarrhea, and nausea, the disease is frequently misdiagnosed and its incidence may be grossly underestimated. Recently, three cases of murine typhus were reported in travelers in Japan, all of which were mild and one did not require antibiotic therapy.

Murine typhus is primarily a benign disease, although some patients develop septic shock and multiorgan failure leading to death. Here, we report a case of severe murine typhus complicated with shock and acute respiratory failure in a Japanese traveler after returning from Thailand. This disease should be considered in differential diagnosis when examining returnees from endemic areas, and antirickettsial treatment should be started without delay for rapid recovery and prevention of further complications when rickettsiosis is suspected.

Case Report

A 56-year-old Japanese man returned from Payao, one of the northern cities of Thailand, to Japan on April 7, 2011. The next day, April 8, fever, headache, and fatigue developed and he visited a local hospital near his home. Despite administration of cefcapene pivoxil, the symptoms continued. He was admitted to Tokyo Metropolitan Bokutoh General Hospital on April 13 under the suspicion of carrying an imported infectious disease such as malaria.

Medical history revealed that the patient previously had appendicitis, a benign colon polyp, and a 5-day fever from unknown causes in Payao, Thailand, where he worked as a Japanese language teacher. A physical examination on admission revealed the following: the patient was conscious, temperature of 36.0°C quickly rising to 39.0°C within 4 hours, blood pressure of 80/55 mmHg, pulse rate of 100/minute and irregular, respiratory rate of 36/minute, conjunctivitis, and small erythematous rashes on the chest. His periphery was cold and capillary refilling time was prolonged. Respiratory, cardiovascular, abdominal, and neurological examinations showed no abnormalities. SpO₂ was 94% (room air). A laboratory examination showed a platelet count of 67 × 10³/µL, total bilirubin...
1.6 mg/dL, aspartate aminotransferase (AST) 150 U/L, alanine aminotransferase (ALT) 154 U/L, lactate dehydrogenase 508 U/L, blood urea nitrogen (BUN) 23 mg/dL, creatinine 1.3 mg/dL, and C-reactive protein 24.27 mg/dL. A urine test showed proteinuria. A blood smear did not reveal the presence of *Plasmodium* species. Two sets of blood cultures were negative. A chest X-ray examination showed left pleural effusion (Figure 1A).

We considered dengue shock syndrome and rickettsiosis, specifically scrub typhus and septic shock due to bacterial infection, in our differential diagnosis, and started fluid replacement therapy along with intravenous administrations of minocycline (100 mg twice a day) and ceftriaxone (2 g twice a day) immediately on the day of admission. However, the patient did not respond to this treatment and fell into acute respiratory distress syndrome (Figure 1B) as early as 4 hours after we started therapy, and was sustained on a ventilator in the intensive care unit. At the time of entry into the intensive care unit, PaO2/FIO2 was 107, CK and CK-MB were within normal range, and BNP was 29.8 pg/mL. Echocardiography showed normal left ventricular function, normal wall movement, and no dilatation of the inferior vena cava diameter. Because he did not present any respiratory symptoms such as cough and sputum, we were not able to collect a sputum sample for a bacterial culture.

Blood samples obtained at the time of admission were examined for dengue, leptospirosis, and rickettsiosis at the National Institute for Infectious Diseases (NIID). On the third day of admission, we received an interim report from the NIID that *Rickettsia* 17 kDa antigen\(^3\) and citrate synthase gene\(^7,8\) (*gltA*) were detected in nested-PCR analysis, whereas *Orientia tsutsugamushi* (56 kDa)\(^9\) was not. Considering the possibility of both typhus and spotted fever bio-groups, we stopped ceftriaxone and switched to ciprofloxacin injections (200 mg twice a day, dosage adjusted for renal dysfunction). His general and respiratory conditions gradually improved, and the patient was extubated on the sixth day of admission. Thereafter, he was treated with oral minocycline (100 mg twice a day) alone for 14 days. Finally, the sequences of two rickettsial genes, 17 kDa antigen (434 bp) and *gltA* (381 bp), detected by nested-PCR were identified as *Rickettsia typhi* Wilmington (NC006142) with 100% homology, whereas the PCR findings for dengue virus and *Leptospira* were negative, as were findings for the NS-1 antigen of the dengue virus, the anti-dengue virus specific-IgM antibody, and anti-leptospiral antibodies against 15 serovars, as shown in microscopic agglutination test results. Unfortunately, we did not store the patient’s serum collected during the recovery phase and did not evaluate serological test results to confirm the diagnosis of murine typhus. However, we carefully performed nested-PCR for increased sensitivity, and targeted multiple gene fragments and sequencing. These results were considered to be reliable for the diagnosis of murine typhus.

**Discussion**

When febrile patients with a recent travel history are examined, it is important to consider malaria, dengue, mononucleosis, rickettsiosis, and typhoid/paratyphoid, whereas malaria, in particular, should be differentiated because of the high risk of mortality.\(^10\) Although each of the initial symptoms (headache, rash, myalgia, arthralgia, diarrhea, nausea) was nonspecific, the triad of fever, headache, and rash might have been clues to indicate rickettsial infection.

In Thailand, both scrub typhus and murine typhus are endemic, with the former being more prevalent and often presenting severe manifestations including...
multiorgan dysfunction, which resemble septicemia from other bacteria and leptospirosis. Because our patient had the triad of rickettsial infection symptoms, it might not have been difficult to consider scrub typhus as a candidate diagnosis from the initial observations upon admission. However, it should be emphasized that murine typhus occasionally brings life-threatening conditions. The mortality rate for murine typhus is reported to be 4% without use of appropriate antibiotics and remains at 1% even when antirickettsial antibiotics are given. Thus, prompt administration of antirickettsial antibiotics is strongly recommended in cases where rickettsiosis, including not only scrub typhus but also murine typhus, is suspected.

Although most cases of murine typhus are self-limited or mild, our patient developed shock and acute respiratory failure immediately after admission. The severity of murine typhus has been associated with male sex, African origin, glucose-6-phosphate dehydrogenase deficiency, older age, delayed diagnosis, hepatic and renal dysfunction, central nervous system abnormalities, and pulmonary compromise. In addition, the risk increases by at least 20% with each day of delay in doxycycline treatment for rickettsial infection after presentation. Our patient matched the parameters of male sex, older age, hepatic and renal dysfunction, and delayed diagnosis. We also investigated glucose-6-phosphate dehydrogenase deficiency, but none was found.

The tetracycline family of drugs, such as minocycline and doxycycline, are used as first-line therapy for rickettsiosis. We considered rickettsiosis as a differential diagnosis in this patient and started treatment including minocycline, while ciprofloxacin was added after obtaining positive results in PCR assays for the rickettsial gltA and 17 kDa genes. In this case, we did not exclude the possibility of infection with other Rickettsia sp. related to Rickettsia japonica, which are known to be present in Thailand, thus minocycline and ciprofloxacin were administered. For fulminant Japanese spotted fever, some physicians in Japan have recommended combination treatment with minocycline and ciprofloxacin. Although the superiority of that combined therapy for Japanese spotted fever, as compared to minocycline alone, has not been confirmed with established evidence, those reports noted an expectation of increased antirickettsial activity with the addition of ciprofloxacin. On the other hand, treatment regimens with doxycycline plus chloramphenicol or ciprofloxacin did not improve the effectiveness of doxycycline in 87 murine typhus patients. Fluoroquinolone treatment has been suggested as an alternative to tetracycline for murine typhus, although reports of both successful treatments and poor clinical response have been presented. Moreover, fluoroquinolone treatment has recently been identified as a risk factor for the development of a severe form of Mediterranean spotted fever. There is no doubt that tetracyclines remain the first choice for the treatment of rickettsiosis, although administration of fluoroquinolone either in combination with or as an alternative to tetracyclines might be individualized in cases in which rickettsiosis is highly probable.

In summary, we treated a case of severe murine typhus complicated by shock and acute respiratory failure after the patient returned to Japan from traveling to Thailand. It is important to consider murine typhus as a part of differential diagnosis when examining returnees from endemic areas, and start administration of tetracyclines without delay for rapid recovery and prevention of complications when rickettsiosis is suspected. The clinical experience with quinolone for murine typhus may be regarded as controversial and additional studies are needed to analyze whether it is effective.

Declaration of Interests

The authors state that they have no conflicts of interest to declare.

References