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The First Fatal Case of Japanese Spotted Fever Confirmed by Serological and Microbiological Tests in Awaji Island, Japan

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Japanese spotted fever is an important rickettsial disease in Japan (1). Japanese spotted fever was first reported by Mahara et al. (2,3) in 1984 in Anan City, Tokushima Prefecture, Japan. Since then, cases of Japanese spotted fever have been reported in many regions of the country. Yuzuruha Mountain in Awaji Island (Figure 1) is one of the areas heavily contaminated with *Rickettsia japonica*, and Japanese spotted

fever cases are reported every summer in this area (4). In the present report, we describe the first fatal case of Japanese spotted fever confirmed by serological and microbiological methods.

A 77-year-old male recognized loss of appetite as the initial symptom on September 2, 2005, which is defined as day 1 of his illness. Rash appeared on the lower thighs on day 2, and a high fever of 38.7°C, dysarthria, and gait disorder on day 4. The patient visited Awaji hospital on day 6, because the symptoms had worsened. The patient claimed that he had worked on farmland, but had not visited a forested area before he developed the illness. He was alert on arrival at the

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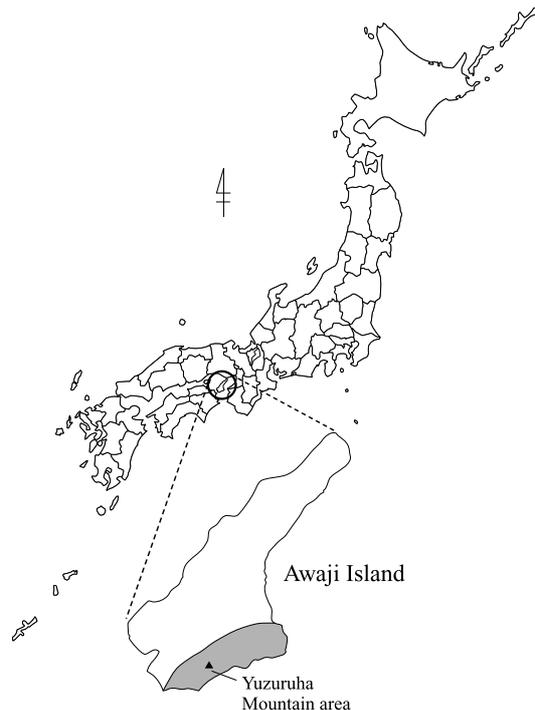


Fig. 1. Location of Yuzuruha Mountain area in Awaji Island.

hospital. At the first visit, other general findings included a height 160 cm, weight 50 kg, body temperature 36.4°C, blood pressure 102/58 mm Hg, pulse rate 86/min and regular, and SpO₂ 97%. There were no abnormal findings in the chest region, and neither abdominal mass nor hepatosplenomegaly was palpable. Lymph node swelling was not found. No neurological abnormality was observed. Diffuse erythema of 7 mm in diameter was present on each bilateral lower thigh, and a bite mark (eschar) of a tick was evident on his anterior right shoulder.

Laboratory data were as follows: red blood cell count $4.48 \times 10^6/\mu\text{l}$, Hb 13.8 g/dl, Ht 39.1%, white blood cell count $12,500/\mu\text{l}$, platelet count $52,000/\mu\text{l}$ – thrombocytopenia observed, FDP 54 $\mu\text{g/ml}$, suggesting concurrent DIC. Mild hepatopathy and dehydration and a marked elevation of CRP at 20.34 mg/dl were observed. Weil-Felix reaction was negative: OX19<1:80, OX2<1:20, and OXK<1:20. Blood sugar level was elevated at 462 mg/dl and HbA1c 6.7%. As an underlying disease, concurrent diabetes was suspected based on the high blood sugar level. Findings from diagnostic imaging were noncontributory.

Because of the presence of an eschar and rash, it was suspected that liver dysfunction and DIC were due to rickettsial infection. Minocycline 200 mg/day, heparin 10,000 units/day, and fluid replacement for dehydration were started for treatment. On day 7, the 2nd day of hospitalization, CRP decreased to 17.7 mg/dl. Physical findings of inflammation started to improve and liver enzyme levels started to normalize. On day 8, blood pressure was 84/48 mm Hg, showing a rapid decline. Thereafter, the patient had repeated bloody stool mixed with red blood clots, and purpura appeared over the entire body. The patient eventually had cardiac arrest and death was confirmed on the same day. The autopsy demonstrated bilateral pleural effusion and oozing hemorrhage from the mucous membranes of the stomach to the large intestine.

DNA was extracted from the blood in EDTA collected at the initial examination. PCR (5) was performed with the R1-

R2 primer combination to detect spotted fever group rickettsia, and a 2nd PCR was then performed using the Rj5-Rj10 primer combination, which specifically amplifies *R. japonica*. Agarose electrophoresis detected the target size of 357 bp as the amplified product. The nucleotide sequence of the amplified product was analyzed by direct sequencing. The nucleotide sequence matched 100% with that of *R. japonica* (GenBank accession no. U83442). Serum IgG and IgM antibody titers were examined against *R. japonica* by indirect immunofluorescence assay. The IgG and IgM titers were 1:320 and 1:80, respectively.

Tsutsugamushi disease and Japanese spotted fever are two diseases caused by rickettsial infection in Japan (1). Within Awaji Island, these diseases occur in different regions: tsutsugamushi disease in the northern part of the island and Japanese spotted fever in the southern Yuzuruha Mountain area (4). This is probably due to the different distribution of the respective vectors. There have been several cases of either disease annually. It is very difficult to differentiate these two diseases based on clinical symptoms, but they can be epidemiologically differentiated to some degree based on the time of year and the geographical location in which they occur. The patient in this study presented all 3 of the major signs for rickettsial infection, eschar, rash, and fever. The patient was clinically suspected to have Japanese spotted fever, according to the time and location of the incidence. Therefore, minocycline administration was started promptly, and the patient's conditions temporarily improved. However, the patient died from hemorrhaging manifestation.

The case fatality ratio of rickettsiosis by the spotted fever group is low. Rocky Mountain spotted fever has an exceptionally high case fatality rate of 3.7% (6). Kodama et al. (7) reported the first fatal case of Japanese spotted fever in 2001 in Awaji Island, but they did not confirm *Rickettsia* infection serologically. The patient in the present report was an elderly person. Although diabetes mellitus was not observed in his medical history, diabetes was thought to be the underlying disease according to the elevated blood sugar level and a high level of HbA1c. Therefore, it is likely that the patient was in an immunocompromised state, and this condition was one of the factors which contributed to the fatal outcome. For those who are old and predicted to have poor prognosis, steroid therapy has been reported to be effective, and the use of an antibacterial agent of the new quinolone group should be considered in combination with minocycline from the start of the treatment (1).

There is no gender difference in the reported cases of Japanese spotted fever. People of all age groups can be affected, but two-thirds of the patients are 50 years old or older. This is probably due to the strong social activity of the elderly people in the mountain village, rather than disease sensitivity. In recent years, the numbers of Japanese spotted fever cases have been increasing (8). Considering the increase in the percentage of the elderly population in semi-mountainous areas in Japan, it is likely that severe and fatal cases of Japanese spotted fever will increase in the future. On the other hand, healthcare providers are not provided enough information regarding this disease. Further, specific serodiagnostic tests and PCR are not widely used. Therefore, it is important to facilitate the use of these diagnostic techniques, and to provide the general residents with sufficient information concerning this disease.

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