

Japanese Spotted Fever: Report of 31 Cases and Review of the Literature

Fumihiko Mahara
Mahara Hospital, Tokushima, Japan

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Spotted fever group (SFG) rickettsioses, which are transmitted by ticks, were long thought not to exist in Japan. Three clinical cases of Japanese spotted fever (JSF) were first reported in 1984. The causative agent was isolated and named *Rickettsia japonica*. Through October 1996, 31 cases were diagnosed as JSF in Tokushima Prefecture. Infected patients typically had acute high fever, headache, and characteristic exanthema; eschar was observed in 90%. After the discovery of JSF, more than a hundred cases were reported in southwestern and central Japan. Recent surveys show ticks to be the most probable vectors. As an emerging infectious disease, JSF is not commonly recognized by clinicians; therefore, even though it has not caused fatal cases, it merits careful monitoring.

The spotted fever group (SFG) rickettsioses, which are transmitted by ticks, have a worldwide distribution. Japanese spotted fever (JSF) is one of the newcomers of this group (1); the first clinical cases were reported in 1984 (2). The causative agent was isolated and named *Rickettsia japonica* (3). Because outbreaks were sporadic and limited, clinical reports concerning JSF, especially from specialists in dermatology and physiology and from general practitioners, were scarce. JSF was first found in Tokushima Prefecture, on the island of Shikoku in southwestern Japan; Tsutsugamushi disease, an important rickettsiosis in Japan, was found there soon afterwards (4). Through October 1996, 31 clinical cases of JSF and 11 cases of Tsutsugamushi disease were diagnosed at Mahara Hospital, Tokushima Prefecture. During the same period, 45 cases of human tick bites were recorded in this JSF-endemic area in the same hospital. This article describes JSF's history, clinical characteristics, and differences from Tsutsugamushi disease and summarizes current information about the epidemiology, vectors, and causative agent of JSF.

History

In the 1980s, clinicians believed that Tsutsugamushi disease (scrub typhus) was the

only rickettsial disease in Japan except for sporadic outbreaks of epidemic typhus in the 1950s. In Tokushima Prefecture, neither disease has been reported in the last two decades. In May 1984, a 63-year-old woman (the wife of a farmer) was hospitalized at Mahara Hospital with high fever and erythematous nonpruritic skin eruptions over the entire body. Antibiotics (β -lactam and aminoglycoside) used for common febrile infections were not effective, but the patient gradually became afebrile in 2 weeks without effective treatment. In May and July 1984, two additional patients with similar symptoms were treated at the same hospital. Doxycycline was markedly effective in these cases. Before the onset of illness, the patients had collected shoots from bamboo plantations on the same mountain. In two of the patients, an eschar was observed. Tsutsugamushi disease was suspected. However, results of Weil-Felix tests showed positive OX2 serum agglutinins, and OXK were negative in all three cases. These results did not indicate Tsutsugamushi disease, but rather OX2-positive infections, i.e., SFG rickettsioses (1).

The cases were subsequently confirmed by complement fixation test with antigens of SFG rickettsiae (5,6). The name Japanese spotted fever was proposed for these infections (7) and has been commonly used since then (8-10). Oriental spotted fever (11) is a synonym for JSF. The causative agent was isolated in 1986 (12) and named *R. japonica* (3).

Address for correspondence: Fumihiko Mahara, 6-1, Aratano, Anan-City, Tokushima 779-15, Japan; fax: 0884-36-3641; e-mail: mahara@ibm.net.

Clinical Features

The clinical features of the 31 patients whose illness was diagnosed as JSF at Mahara Hospital from 1984 to October 1996 were analyzed. The disease developed abruptly, with the common symptoms of headache (25 [80%] of 31 patients), fever (31 [100%] of patients), and shaking chills (27 [87%]). Other major objective symptoms of JSF included skin eruptions (31 [100%]) and tick bite eschars (28 [90%]). Most patients (28 [90%]) complained of malaise; joint and muscle pain or numbness of the extremities was rarely mentioned. In the acute stage, remittent fever accompanied by shaking chills was frequently observed. In severe cases, high fever (40°C or more) continued for several days (Figure 1). The maximum body temperature was 38.5°C to 40.8°C (mean 39.5°C), which was higher than that seen in patients with Tsutsugamushi disease (38.5°C ~ 39.1°C). With abrupt high fever or, a few days after onset, fever of unknown origin, the characteristic erythemas developed on the extremities and spread rapidly (in a few hours) to all parts of the body including palms and soles, without accompanying pain or itching. These eruptions were the size of a grain of rice or soybean, and the margin of each of the spots was unclear (Figure 2). The erythemas became remarkable during the febrile period and tended to spread more over the extremities than the trunk. Palmar erythema, a characteristic finding not seen in Tsutsugamushi disease, disappeared in the early stage of the disease. The erythemas became petechial after 3 to 4 days, peaked in a week or 10 days, and disappeared in 2 weeks. However, in severe petechial cases, the brown pigmentation remained for 2 months or more. Eschar was observed on the hands, feet, neck, trunk, and shoulders of patients (Figure 3). This eschar generally remained for 1 to 2 weeks, but in some cases it disappeared in a few days. Eschars in JSF patients are smaller than those seen in patients with Tsutsugamushi disease and may be missed without careful observation. Regional or generalized lymphadenopathy, which is observed in almost all cases of Tsutsugamushi disease, was not remarkable in JSF patients. Swelling of the liver and spleen was observed in a few patients. One patient had cardiomegaly (5), and in another area, a patient had central nervous system involvement (13).

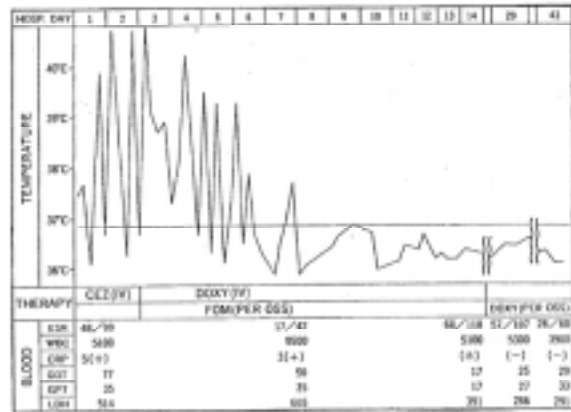


Figure 1. Fever and clinical course, 62-year-old woman.

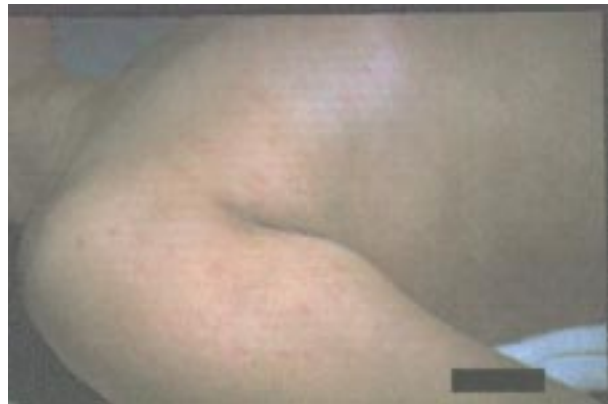


Figure 2. Skin eruptions, hospital day 3.

Laboratory Examinations

The results of laboratory examinations of JSF patients are almost the same as those of patients with common SFG rickettsioses. During clinical examinations at the initial stage of the disease, urinalyses registered a slight positive reading for protein and occult blood, which may lead to a misdiagnosis of urinary infection. In the acute stage, leukocytosis may also be found with leukopenia (3,600~12,800), and a left shift in leukocyte count was observed. Thrombocytopenia (6.8~35.3) may also be found. In week 1 to 2, leukocyte counts increased slightly, and lymphocyte counts tended to increase. Among biochemical examinations, C-reactive proteins were strongly positive, and liver functions were slightly impaired but returned to normal in 2 to 3 weeks.



Figure 3. Small and shallow eschar on admission, which disappeared in a few days.

Serologic Results

Serodiagnosis for JSF is usually performed by the indirect immunoperoxidase (IP) or immunofluorescence (IF) techniques, with antigens prepared from *R. japonica* or other SFG rickettsiae. With the IP test, IgG and IgM antibodies were detected in the sera beginning on day 9 after the onset of fever; titers of IgG antibodies were higher than those of IgM antibodies (14). The IF test had similar results (15). In the 31 clinically diagnosed cases of JSF in Tokushima Prefecture at Mahara Hospital, all patients had significant changes in serum IP antibody titers to *R. japonica*, and 27 (87%) had significant changes in OX2 agglutinin titers by the Weil-Felix technique (10,14; F. Mahara, unpub. data).

Treatment

Antibiotics such as penicillins, β -lactams, or aminoglycosides, commonly used in the empiric treatment of febrile disease, were completely ineffective, but doxycycline and minocycline were markedly effective in treating the JSF patients (16).

On the first day of hospitalization in one patient with severe disease (Figure 1), fever of more than 40°C with shaking chills persisted after the antibiotics cefazolin and fosfomycin were administered. The general condition of the patient worsened and on the morning of the third day, generalized edema and confusion developed. On day 3, the patient was given drip infusion of doxycycline 300 mg per day, which was dramatically effective; the fever decreased to 38°C during the first drip infusion.

In an in vitro study, minocycline was the most effective antibiotic against *R. japonica*, followed by other tetracycline antibiotics (17,18). In contrast, the sensitivity to β -lactam and penicillin was lower or negligible, but quinolones were effective against the JSF agent (18). Three patients were treated with a new quinolone (tosufloxacin 300 mg per day in three divided doses per os), which proved effective in two cases (9). Patients with dehydration received drip infusion of doxycycline or minocycline (200 mg to 300 mg per day for 3 to 7 days), and after becoming afebrile, received 200 mg per day 2 divided doses to prevent relapse. Patients suspected of having JSF should receive empiric therapy with minocycline or doxycycline without waiting for serologic confirmation of illness.

Epidemiology

From 1984 to 1995, 144 cases of JSF were reported by the National Institutes of Health in Japan (19; Figure 4). Case reports included only the number of cases and prefectures where cases were reported, including Tokushima Prefecture. According to this information, JSF-endemic prefectures are located along the coast of southwestern and central Japan in a warm climate (Figure 5). The landscape is diverse, including bamboo plantations, crop fields, coastal hills, and forests (20). Of the 31 JSF patients in Tokushima Prefecture, nine were male, and 22 were female. Ages were 4 to 78 years, but most patients (68%) were 60 to 70 years old. The onset of the disease was 2 to 8 days after work in the fields. In this prefecture, farmers work in the forest to gather bamboo shoots in the spring and chestnuts in the autumn; cases occurred from April to October

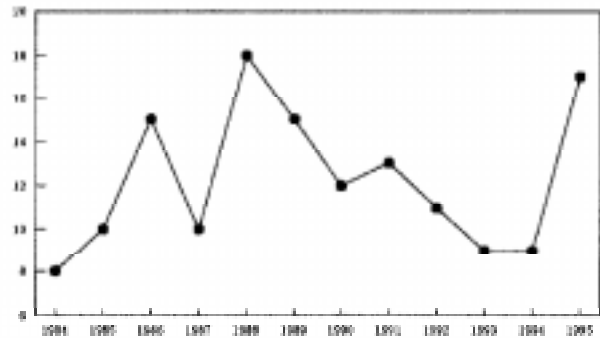


Figure 4. The number of Japanese spotted fever patients in Japan (1984–1995).

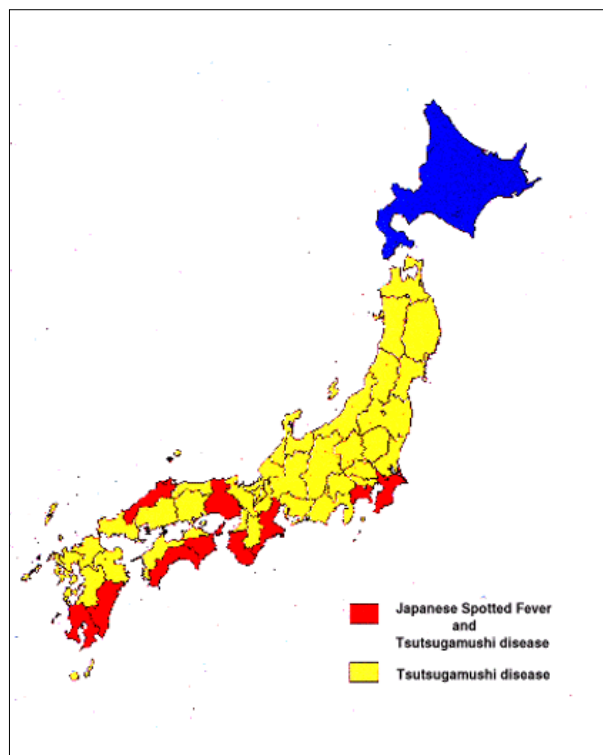


Figure 5. Geographic distributions of JSF and Tsutsugamushi disease in Japan.

(6,18; Figure 6). In this area, we can distinguish seasonal differences in the occurrence of JSF and Tsutsugamushi disease; whereas JSF occurs from spring to autumn, Tsutsugamushi disease occurs in winter (November–February). Although seasonal differences occur in the western parts of Japan, the prevalent seasons for Tsutsugamushi disease vary in other parts of Japan (21).

Like other SFG rickettsioses, JSF is presumed to be transmitted by a tick bite. The high proportion of patients with tick bite eschars supports this hypothesis. Thirteen JSF patients (28.9%) recalled tick bites before the onset of illness; however, the ticks had been lost, and no specimens from the patients were available for further study. From 1984 to October 1996, 45 persons with tick bites were recorded at Mahara Hospital (Table 1). Identified ticks included three genera and eight species.

Three genera and six species of ticks have been reported as positive for *R. japonica* in JSF-endemic areas (Table 2). Hemolymph samples from *Dermacentor taiwanensis*, *Haemaphysalis flava*, *Haemaphysalis formosensis*, *Haemaphysalis hystricis*, *Haemaphysalis longicornis*, and *Ixodes*

ovatus were positive when tested by the IP technique using a species-specific monoclonal antibody against *R. japonica* (22). *R. japonica* was also detected by IF in the hemolymph of *H. longicornis* (23). A polymerase chain reaction (PCR) technique using species-specific primers detected *R. japonica* in *H. hystricis* (24), *H. flava*, and *I. ovatus* (25). The agent has also been detected in *H. longicornis* by restriction fragment length polymorphism of PCR product (23). Of these, *H. flava*, *H. longicornis*, and *I. ovatus* commonly feed on humans in Japan (26). Recent tick surveys in Japan have identified two serotypes or species of SFG rickettsial isolates other than *R. japonica*, which are of uncertain clinical significance (27,28).

Pathogen

The etiologic agent was first isolated from a patient (in Kochi Prefecture) in 1986 (12). In 1987, the causative rickettsia was also isolated from a JSF patient in Tokushima Prefecture (29-31). The former isolate is the type strain YH

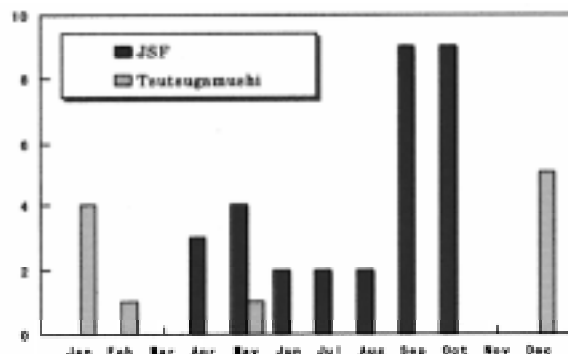


Figure 6. Seasonal prevalence of Japanese spotted fever and Tsutsugamushi disease.

Table 1. Cases of human tick bites, Mahara Hospital, 1984–1996

	Female	Male	Nymph	Larva	Total
<i>Haemaphysalis flava</i>	1		4		5
<i>Haemaphysalis longicornis</i>	8	1	3	2	14
<i>Amblyomma testdunarium</i>	4	1	12		17
<i>Ixodes ovatus</i>	1				1
<i>Ixodes nipponensis</i>	4				4
<i>Ixodes persulcatus</i>			2		2
<i>Ixodes tanuki</i>	1				1
<i>Haemaphysalis kitaokai</i>	1				1
Totals	20	2	21	2	45

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Table 2. Reported tick species positive for *Rickettsia japonica* and their prevalence in endemic disease areas

Tick species	No. positive/no. examined		
	Tokushima	Kochi	Kanagawa
<i>Dermacentor taiwanensis</i>	3/5 ^a , 1/1 ^b	-	-
<i>Haemaphysalis flava</i>	6/36 ^a	3/10 ^a	1-3/90 ^c
<i>Haemaphysalis formosensis</i>	-	10/16 ^a	-
<i>Haemaphysalis hystricis</i>	+ ^d	5/9 ^a	-
<i>Haemaphysalis longicornis</i>	-	1/1 ^a , 6/9 ^e , 5-33/33 ^f	-
<i>Ixodes ovatus</i>	1/13 ^a	-	1/16 ^c

^aHemolymph test by immunoperoxidase stain using *R. japonica*-specific monoclonal antibody (22).

^bIsolation (28).

^cPolymerase chain reaction (PCR) using the primers designed for amplifying the genomic DNA from only *R. japonica* (25).

^dPCR method same as the above (24). Number was not shown.

^eHemolymph test by immunofluorescein stain using *R. japonica*-specific monoclonal antibody (23).

^fRestriction fragment length polymorphism of PCR product (23).

(ATCC VR-1363), later named *R. japonica*, a new SFG rickettsia; the latter strain (Katayama) was the first isolate from JSF-endemic areas outside Kochi (3,32). The Katayama strain type and *R. japonica* were demonstrated by serologic analysis using monoclonal antibodies (33). Sero-typing by use of the reciprocal cross-reactions of mouse antisera to six human isolates from Tokushima and the type strain YH or *R. japonica* also indicated that these are the same species (34). In 1988, another strain was isolated from a patient in Awaji Island, Hyogo Prefecture, which is considered a new area of JSF-endemic disease (35).

Recently, an isolate from a febrile patient in Wakayama Prefecture was also reported as *R. japonica* (36). In an electron microscopy study, *R. japonica* were generally recognized as short rods or pleomorphic coccobacillary forms less than 2 μm in length and 0.5 μm in diameter and could be found not only in the cytoplasm but also in the nuclei of the host cells (37). A multilayered mesosome-like structure was observed in the rickettsiae multiplying in a host cell (38). This unique structure has not been reported in other species except in *Rickettsia prowazekii* (39). After the initial isolation, at least 20 rickettsial strains have been isolated from JSF patients by cell culture techniques or nude mouse passage in Tokushima, Kochi, Hyogo, Chiba, and Wakayama

Prefectures. However, it has not been determined if their strains differ in virulence.

Ten diseases caused by SFG rickettsiae have been reported in humans (40): Rocky Mountain spotted fever, Mediterranean spotted fever, Siberian tick typhus, African tick bite fever, Queensland tick typhus, Japanese spotted fever, Israeli spotted fever, Astrakhan spotted fever, Flinders Island spotted fever, and rickettsialpox. The clinical symptoms of JSF—a triad of high fever, skin eruptions, and tick bite eschar—are similar to those of typical SFG rickettsioses. With regard to skin eruptions, eschar, and severity of the disease, JSF is more akin to Mediterranean spotted fever and Siberian tick typhus than to Rocky Mountain spotted fever. Recent tick surveys indicated that the most probable vectors of JSF are *H. flava*, *H. longicornis*, and *I. ovatus*.

In Japan, the clinical features of JSF are similar to those of Tsutsugamushi disease; however, close clinical observation exposes the differences between the two diseases. Widespread outbreaks of Tsutsugamushi disease have been reported repeatedly in recent years (21). No fatal cases of JSF have been reported. However, death rates from other SFG rickettsioses (approximately 2.5% for Mediterranean spotted fever [41] and 3% to 7% from Rocky Mountain spotted fever [42]) suggest that unless JSF is treated appropriately, it can pose the same risk. If JSF is suspected, empiric treatment should begin without delay during the early stages of disease.

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Dr. Mahara is chief director of Mahara Hospital, Tokushima, Japan. He serves as a counselor of the Japanese Association for Infectious Diseases and is a member of the International Eurasian Academy of Sciences.

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