

SCRUB TYPHUS IN JAPAN: EPIDEMIOLOGY AND CLINICAL FEATURES OF CASES REPORTED IN 1998

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Abstract. Surveillance for scrub typhus was conducted in Japan in 1998 using a questionnaire. A total of 462 cases were reported. Scrub typhus occurred in both the fall and spring in the northern part of Honshu (the main island), and in the fall in the central part of Honshu and on the island of Kyushu. The occurrence of the disease varied with age, gender, and activity. Seventy-six percent of the patients were more than 51 years old, and 36% and 16% of the patients were engaged in farm work and forestry, respectively. Fever, rash, and eschar were detected in 98%, 93%, and 97% of the patients, respectively. Elevated levels of C-reactive protein, aspartate transaminase, and alanine transaminase were detected in 96%, 87%, and 77% of the patients, respectively. Disseminated intravascular coagulation developed in 34 cases and had a unique regional distribution. This study shows the status of scrub typhus in Japan in 1998 and provides important information for diagnosis and prevention.

INTRODUCTION

Tsutsugamushi disease, also known as scrub typhus, is a rickettsial disease caused by *Orientia tsutsugamushi*.¹ This organism is transmitted by infected trombiculid mites. Scrub typhus is widely found in Asian countries, including Japan.^{2,3} When the rickettsia is transmitted by bite from an infected mite to a human, it begins to grow at the location of the bite and a characteristic skin lesion known as an eschar is formed. The rickettsia then spreads systemically via the hematogenous and lymphatogenous routes, and the infected human develops various systemic symptoms and reactions including fever, rash, lymphadenopathy, elevations of C-reacting protein (CRP) and liver enzymes.³⁻⁵

Scrub typhus was first known as a life-threatening, endemic disease that occurred mainly in summer along rivers in the Tohoku-Hokuriku area of Japan in the northern part of the Honshu (the main island). This is known as the classic type, which is transmitted by the mite *Leptotrombium akamushi*. In 1948, soldiers from the United States stationed in this area after World War II developed an unknown fever. This disease was later identified as scrub typhus. This disease was eventually detected on the Izu Shichitou islands (Shichitou fever), in Chiba prefecture (Hatsuka fever), and in several other prefectures. This newly recognized scrub typhus is called new type and is transmitted by the mites *L. scutellare* and *L. pallidum*. This new type has now been recognized in almost all areas of Japan, except in Okinawa and Hokkaido prefectures. The classic type seems to be no longer present.³

Since 1989, the Working Group for Tsutsugamushi Disease Surveillance in Japan of the Association of Public Health Laboratories for Microbiological Technology, which was organized by National Institute of Infectious Diseases and public health laboratories in prefectures of Japan, has been collecting information on scrub typhus by questionnaires. In the present study, scrub typhus patients reported in 1998 were analyzed for epidemiologic information and clinical features. This study provides information of the status of scrub typhus in Japan in 1998.

MATERIALS AND METHODS

Questionnaire. The working group for scrub typhus surveillance of Japan developed a questionnaire about scrub typhus in 1998. The questionnaire was answered by doctors in hospitals, and the staffs of health centers and public health laboratories in the prefectures of Japan. The questionnaire included questions about patients' 1) demography: age and sex; 2) epidemiologic data: date, places (prefectures and areas), and activities at the time of infection; 3) clinical signs and symptoms: eschar, fever, rash, lymphadenopathy, malaise, headache, myalgia, hepatomegaly, and disseminated intravascular coagulation (DIC); 4) laboratory findings: CRP, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), white blood cell (WBC) counts, proteinuria and occult blood in urine; and 5) diagnosis: methods and results of serologic tests.

Data analysis. All data were analyzed using Visual dBASE 5.5J software (Borland International, Inc., Scotts Valley, CA). In calculations of percentages, denominators were modified when answers for any items in the questionnaire were missing. The percentages of cases with DIC, available WBC counts, and available levels of CRP, AST, and ALT were compared for Tohoku-Hokuriku, Kanto (in the central part of Honshu), and Kyushu. Differences in percentages among areas were tested by the chi-square test. A difference was considered statistically significant when the *P* value was less than 0.05.

RESULTS

Cases of scrub typhus. In 1998, 462 cases of scrub typhus were reported. Four hundred-eight cases (88%) were confirmed by serologic tests after the provisional diagnosis by clinicians, while 54 cases (12%) were diagnosed by clinicians based on clinical symptoms only.

Distribution of cases. The distribution of cases in nine areas of Japan is shown in Figure 1. The largest number of cases in Japan was in Kyushu, where 234 cases (51%) were reported. In Tohoku-Hokuriku and Kanto, 123 (27%) and 87 (19%)

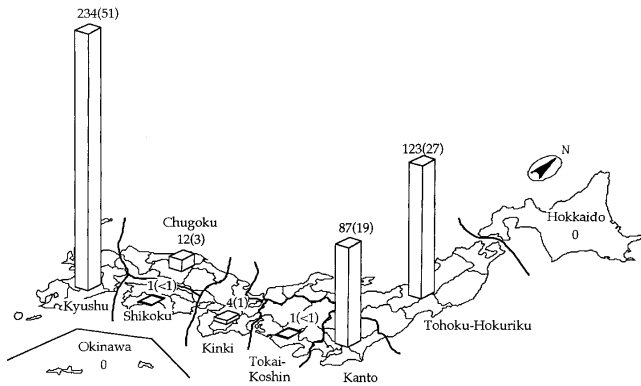


FIGURE 1. Distribution of cases of scrub typhus in Japan in 1998. A total of 462 cases of scrub typhus were reported. The number of cases (%) in each area is shown above each bar.

cases were reported, respectively. The cases in these three areas accounted for 97% of the cases in Japan. The remaining cases were distributed as follows: Chugoku 12 (3%), Kinki 4 (1%), Tokai-Koshin 1 (<1%), and Shikoku 1 (<1%), respectively.

Seasonal differences in the occurrence of cases. Monthly changes in the number of reported cases are shown in Figure 2. There were two peaks: a big large one in November and a small one in May. The large peak represents the cases in Kanto and Kyushu and a few cases in Tohoku-Hokuriku. The small peak represents mainly the cases in Tohoku-Hokuriku.

Sex and age distributions of cases. The sex and age distributions of the cases are shown in Table 1. Two hundred thirty-two cases (50%) were males and 230 cases (50%) were females. Fourteen (3%) cases were 0–25 years old, 94 (21%) were 26–50 years old, 275 (62%) were 51–75 years old, and 63 (14%) were ≥ 76 years old. The youngest and oldest cases were four and 91 years old, respectively. Fifty percent of the

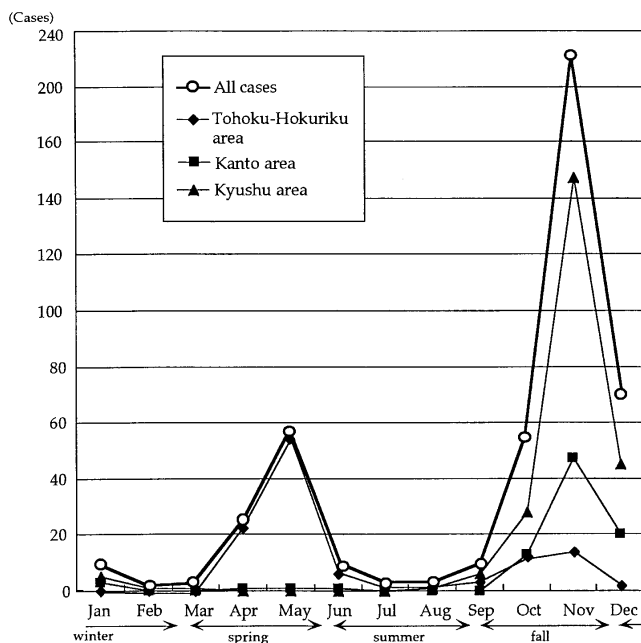


FIGURE 2. Seasonal cases of scrub typhus in Japan in 1998.

TABLE 1
Sex and age distributions of scrub typhus cases

Age (years)	No. of cases (%)*	Sex distribution (M:F) (%)
0–25	14 (3)	7:7 (50:50)
26–50	94 (21)	54:40 (57:43)
51–75	275 (62)	135:140 (49:51)
≥76	63 (14)	27:36 (43:57)
Unknown	16	9:7 (56:44)
Total	462	232:230 (50:50)

* Sixteen unknown cases are not included in calculations of the percentage.

cases were males and 50% were females in those 0–25 years old, 57% were males and 43% were females in those 26–50 years old, 49% were males and 51% were females in those 51–75 years old, and 43% were males and 57% were females in those ≥ 76 years old.

Activities of cases at the time of infection. The activities that the cases performed at the time of infection were farm work in 155 cases (36%), forestry in 57(16%), collecting edible wild plants in 48 (12%), recreation in 27 (7%), construction work in 15 (4%) and other activities in 106 (26%) (Table 2). Activities at the time of infection were not known for 54 cases. Thirty-seven percent of the cases involved in farm work at the time of infection were males and 63% were females, 82% of those involved in forestry were males and 18% were females, 60% of those involved in collecting wild edible plants were males 60% and 40% were females, 67% of those involved in recreation were males and 33% were females, and 87% of those involved in construction were males and 13% were females (Table 2).

Clinical symptoms. The clinical symptoms of the patients are shown in Table 3. Three major clinical symptoms, fever, rash, and eschar, were observed in 98%, 93%, and 87% of the cases, respectively. Malaise, lymphadenopathy, headache, myalgia, DIC, and hepatomegaly were observed in 63%, 52%, 46%, 16%, 14%, and 3% of the cases, respectively.

Laboratory findings. Laboratory findings of the patients are shown in Table 4. Elevated levels of CRP, LDH, GOT, and GPT were observed in 96%, 92%, 87%, and 77% of the cases, respectively. Proteinuria and occult blood in the urine were observed in 59% and 44% of the cases, respectively. Normal (4,000–9,000 cells/ml), decreased (< 4,000 cells/ml) and increased (> 9,000 cells/ml) WBC counts were observed in 55%, 26%, and 19% of the cases, respectively.

Geographic differences in clinical symptoms and laboratory findings. Elevated levels of CRP, AST, and ALT, decreased WBC counts, and DIC, which were closely related to the severity of the illness, were compared in Tohoku-Hokuriku, Kanto, and Kyushu (Figure 3). The percentages of cases with DIC and a decreased WBC count were significantly higher in Tohoku-Hokuriku than in Kanto and Kyushu ($\chi^2 = 23.7$,

TABLE 2
Activities of the patients at the time of scrub typhus infection

Activities	No. of cases* (%)	Sex distribution (M:F) (%)
Farm work	155 (44)	57:98 (37:63)
Forest work	57 (16)	47:10 (82:18)
Collecting wild edible plants	48 (13)	29:19 (60:40)
Recreation	27 (8)	18:9 (67:33)
Construction	15 (4)	13:2 (87:13)
Others	54 (15)	45:61 (42:58)

* Fifty-four unknown cases are not included.

TABLE 3
Clinical symptoms in scrub typhus patients

Symptoms	Percentage (cases/total cases*)
Fever	98 (434/443)
Rash	93 (411/444)
Eschar	87 (391/452)
Malaise	63 (321/462)
Lymphadenopathy	52 (223/426)
Headache	46 (225/462)
Myalgia	16 (81/465)
DIC†	14 (34/237)
Hepatomegaly	3 (16/462)

* Total cases does not include unknown cases.

† DIC = Disseminated intravascular coagulation.

degrees of freedom [df] = 2, $P < 0.001$ for DIC and $\chi^2 = 6.59$, df = 2, $P < 0.037$ for a decreased WBC count). Furthermore, percentages of cases with elevated levels of CRP, AST, and ALT were higher in Tohoku-Hokuriku than in Kanto and Kyushu, although these differences were not statistically significant.

DISCUSSION

We have analyzed the epidemiologic aspects and clinical features of scrub typhus in Japan in 1998. A total of 462 cases were reported, and 97% of the cases were found in three areas: Tohoku-Hokuriku, Kanto, and Kyushu.

Monthly changes in the number of cases showed epidemic periods in the spring and fall. The spring epidemic period was from April to June, with a small peak in May, while the fall epidemic period was from September to January, with a large peak in October. The cases occurred in Tohoku-Hokuriku in both the spring and fall, while those in Kanto and Kyushu occurred mainly in the fall. These results show the different epidemic periods in individual areas. The epidemic periods are influenced by the activities of infected mite; therefore, they may be influenced by climate and temperature.

Monthly changes in the number of the cases in Tohoku-Hokuriku were different from those in Kanto and Kyushu. This may be due to different mites inhabiting individual areas. *Leptotrombium pallidum* is dominant in Tohoku-Hokuriku, while *L. scutellare* is dominant in Kanto and Kyushu.^{3,6} These mites infest mammals once in their life cycle.⁷ Both *L. pallidum* and *L. scutellare* infest mammals, including humans, in

TABLE 4
Laboratory findings in scrub typhus patients

Findings*	Percentage (cases/total cases)†
CRP elevation	96 (264/274)
LDH elevation	92 (246/267)
AST elevation	87 (246/284)
ALT elevation	77 (216/282)
Proteinuria	59 (158/276)
Occult blood in urine	44 (85/195)
WBC count	
Normal	55 (163/297)
Decreased	26 (77/297)
Increased	19 (57/297)

* CRP = C-reactive protein; LDH = lactate dehydrogenase; AST = aspartate aminotransferase; ALT = alanine aminotransferase; WBC = white blood cell; Normal = 4,000–9,000 cells/mL; Decreased = <4,000 cells/mL; Increased = >9,000 cells/mL.

† Total cases does not include unknown cases.

the fall. Only *L. pallidum* can survive cold temperatures. It hibernates under the snow during the winter in Tohoku-Hokuriku, and then awakes and infests mammals in the spring when the temperature increases.^{6,8,9} More cases were reported in the spring than in the fall in Tohoku-Hokuriku, while another report showed that the number of the mites that infested rodents did not differ between fall and spring.⁶ The reason of this discrepancy is unknown, and further analysis should be performed.

Some of the cases were engaged in farm work (44%) and forestry (16%). This suggests that these activities in the infected areas increase the duration of exposure and the possibility of infestation by infected mites. Transfer of *O. tsutsugamushi* from an infected mite to a human takes more than six hours.^{8,9} Thus, long exposure in the infected areas during the epidemic periods increases the risk of infection. For prevention, people should change clothes and wash after their activities. In addition, an increase in outdoor activities, such as recreation and collecting edible wild plants, may increase the risk of infection.

The occurrence of scrub typhus varied with age, gender, and activity. Our results show that the rates of infection in males in Japan in 1998 were 51% in those 0–24 years old, 50% in those 25–49 years old, 48% in those 50–74 years old, and 35% in those ≥ 75 years old. In addition, the percentage of females engaged in farm work was higher than that of males, while the percentage of males engaged in other activities was higher than that of females. In the present study, 76% of the patients were more than 51 years old. Census data indicate that 35% of the population in Japan in 1998 were people ≥ 50 years old. Many of the patients with scrub typhus were persons of middle and advanced age.

Fever, rash, and eschar are the most common symptoms of scrub typhus, and are important in the clinical diagnosis of this disease. As expected, these symptoms were also the most common ones observed in the present study. However, eschar, the most characteristic symptom, was not observed in 13% of the patients, although previous reports indicated that nearly 100% of the patients had eschar.^{10–13} Since many patients complained of malaise and headache, some cases with-

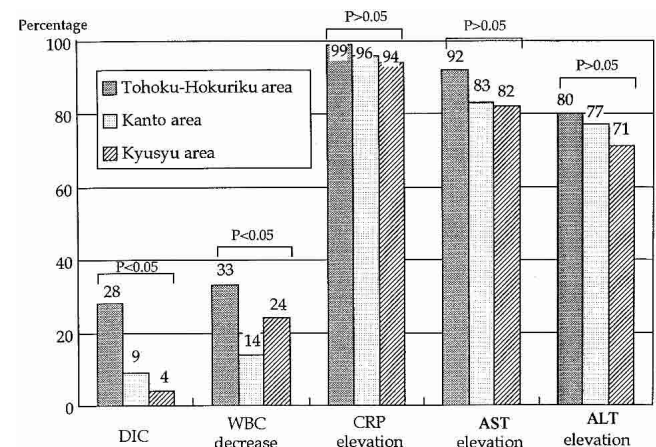


FIGURE 3. Differences in clinical features of scrub typhus among geographical regions of Japan in 1998. DIC = disseminated intravascular coagulation; WBC = white blood cells (count < 4,000 cells/ml); CRP = C-reactive protein; AST = aspartate aminotransferase; ALT = alanine aminotransferase.

out eschar may have been misdiagnosed as the common cold or another febrile illness. In the present study, lymphadenopathy was detected in 52% of the patients, consistent with previous reports of 30–80%.^{10–13} It is possible that the immune response in these patients without lymphadenopathy was mild; therefore, the lymphadenopathy would not have been detected. This immune response may be related to the status of infection with *O. tsutsugamushi*.

Elevated levels of CRP and LDH, an indication of hepatic dysfunction and inflammation, were observed in more than 90% of the patients. Elevated levels of AST and ALT were found in approximately 80% of the patients. In addition, proteinuria and occult blood in the urine were found in approximately half of the patients, suggesting that they are not rare symptoms. New guidelines for the clinical diagnosis of scrub typhus that include this information should be established.

Disseminated intravascular coagulation developed in 34 patients, indicating that scrub typhus is a life-threatening disease. The percentage of the cases with DIC was higher in Tohoku-Hokuriku than in Kanto and Kyushu. Furthermore, the percentage of the cases with elevations of CRP, AST, and ALT levels was slightly higher in Tohoku-Hokuriku than in Kanto and Kyushu. These results suggest that scrub typhus in Tohoku-Hokuriku was a more serious problem than in the other areas of Japan. In addition, the percentage of cases with decreased WBC counts was highest in Tohoku-Hokuriku. Previous reports based on studies with mice showed that the isolates of *O. tsutsugamushi* in Tohoku-Hokuriku were more virulent than those in other areas.^{3,14} It was also reported that *L. pallidum*, a vector involved in the transmission of a virulent strain of *O. tsutsugamushi*, was found mainly in Tohoku-Hokuriku, whereas *L. scutellare*, a vector involved in the transmission of a less virulent strain, was found in other areas. The differences in virulence of the isolates from Tohoku-Hokuriku and other areas should be investigated.^{3,14} In addition, the incidences of scrub typhus per one million people in the areas studied were 17 in Kyushu, 8.0 in Tohoku-Hokuriku, and 2.2 in Kanto area. However, it is not known if there is a relationship between incidence and disease severity.

In conclusion, this study reports the epidemiologic aspects and clinical features of scrub typhus in Japan in 1998. Information obtained in the present study will provide better insights into the diagnosis, treatment, and prevention of this disease in Japan. Surveillance of this disease should be continued to obtain a better understanding of its current status. In addition, guidelines for prevention, diagnosis, and treatment should be established.

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