Tokai J Exp Clin Med., Vol. 26, No. 1 , pp.19-24, 2001

Tsutsugamushi Disease in Kanagawa Prefecture, Japan: Clinical Report of Two Cases and Survey of Other Incidences in 1998

Hirotake OZAKI, Takashi MATSUYAMA, Kaori HIRABAYASHI, Mariko IIZUKA, Kazushi URANO, Yo KAWAKUBO, Seiitsu KANNO, Akira OZAWA, Muneo OHKIDO, Fumio HIROTA*, and Noriyasu NAGASHIMA**

Department of Dermatology, Tokai University School of Medicine,
** First Department of Internal Medicine, Hadano Red Cross Hospital,*
*** Nagashima Skin Clinic, Hadano-city, Kanagawa Pref.*

(Received December 16, 2000; February 14, 2001)

Tsutsugamushi disease is characterized by the early appearance of a black crust at the bitten area and the subsequent development of macular or macropapular rush on the whole body with high fever. While treatment with tetracycline derivatives and chloramphenicols is effective, delayed diagnosis or inappropriate treatment will lead to fatality. In this report, we describe two typical cases of tsutsugamushi disease and discuss other incidences in Kanagawa Prefecture, Japan, in 1998. One of the present two patients was diagnosed to be a case of the new type by Kawasaki strain of *Rickettsia tsutsugamushi*, while responsible strain was not identified for the other case. Since the disease is spreading widely even to suburban areas, we emphasize the need to consider the possible diagnosis of tsutsugamushi disease in patients with generalized eruption and high fever.

Key words : Tsutsugamushi disease, Fever, Skin rush, Minocycline hydrochloride

INTRODUCTION

Tsutsugamushi disease occurs widely in various countries in South-East Asia and South Pacific Ocean islands. Since the Meiji era, the disease has been endemic to Niigata, Akita, and Yamagata and considered highly mortal. Cases of tsutsugamushi disease have also been reported in the Izu Seven islands and the foot of Mt. Fuji since 1948. Two types of tsutsugamushi disease are recognized with differences in the epidemiology, the time of incidence, and mortality. One is the classical type with high mortality, caused by Gilliam, Karp, or Kato strain of *Rickettsia tsutsugamushi*, and endemic to the Tohoku area. The other is the new type, which is characterized by low mortality and occurs in areas other than the Tohoku area. Causative agents are Kawasaki and Kuroki strains of *Rickettsia tsutsugamushi.*

Recently, tsutsugamushi disease has been widely distributed to a number of areas in Japan [5, 6, 7]. A continuing increase in incidence has been noted in Kanagawa Prefecture, due likely to the development of traffic networks, the recent outdoor sports boom, and the extension of residential and business areas into the forest. Because tsutsugamushi disease can take a fatal course when diagnosis is delayed, we urge to consider the possible diagnosis of tsutsugamushi disease in patients with general eruption and fever.

CASE REPORTS

Case 1: Female, 48 years old
Chief complaint: Generalized eruption
First visiting date: November 9, 1998
Familial and past histories: None special.
Present history: She felt a pain on the right femoral region when she sat on a bench in a golf course in Matsuda City, Kanagawa Prefecture, on November 2, 1998. She developed fever of about 39℃ on Nov. 4, 1998, which persisted in spite of the treatment by a nearby practitioner. Because edematous ery-

Hirotake OZAKI, Department of Dermatology, Tokai University School of Medicine, Bohseidai, Isehara, Kanagawa 259-1193, Japan Tel: 0463-93-1121 Fax: 0463-93-9387

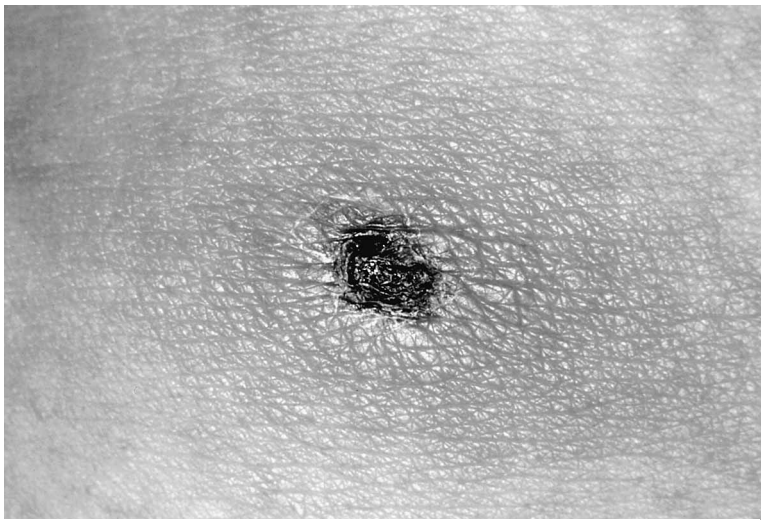

Fig. 1 Skin lesion of Case 1 patient. Upon admission, a 7 × 15 mm crust with a red induration was found on the right femoral region.

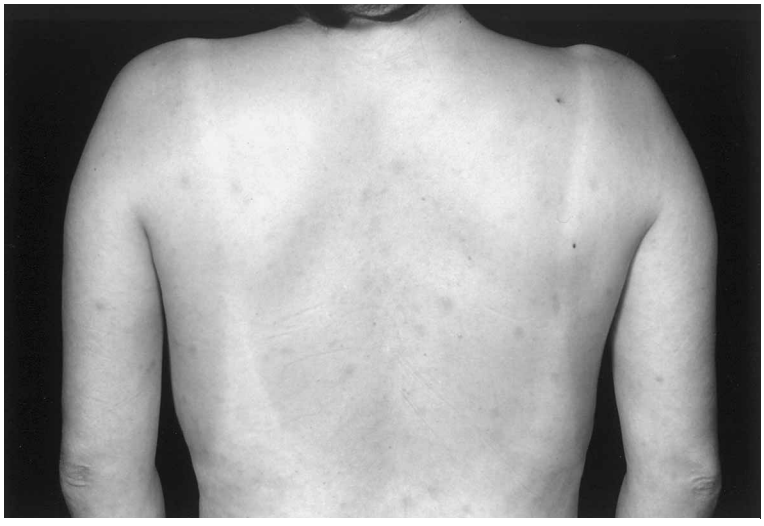

Fig. 2 Systemic skin lesion of Case 1 patient. Diffuse, infiltrative erythemas with a diameter of 5 to 20 mm were noted on the whole body including the face.

themas developed on the whole body, she was referred to our department.

Clinical findings: A 7 × 15 mm black crust with a red induration was noted on the right femoral region (Fig. 1). Diffuse, undefined edematous erythemas with a diameter of 5 to 20 mm were noted on the whole body including the face (Fig. 2). No superficial lymph node was palpable.

Laboratory findings: CBC showed a slight reduction in WBC to 3.91×10^3, while no abnormality was found in white blood cell differential count. Blood biochemistry showed that GOT, GPT, γ-GTP, and CRP were all high at 83 U/l, 103 U/l, 121 U/l, and 3.98 mg/dl, respectively. Erythrocyte sedimentation rate was slightly high at 29 mm/h, while coagulability was only slightly prolonged as indicated by APTT of 40.9 sec, PT of 12.8 sec, fibrinogen of 417 mg/dl, and FDP of 90 μg/dl.

Pathological findings: Skin biopsy was per-

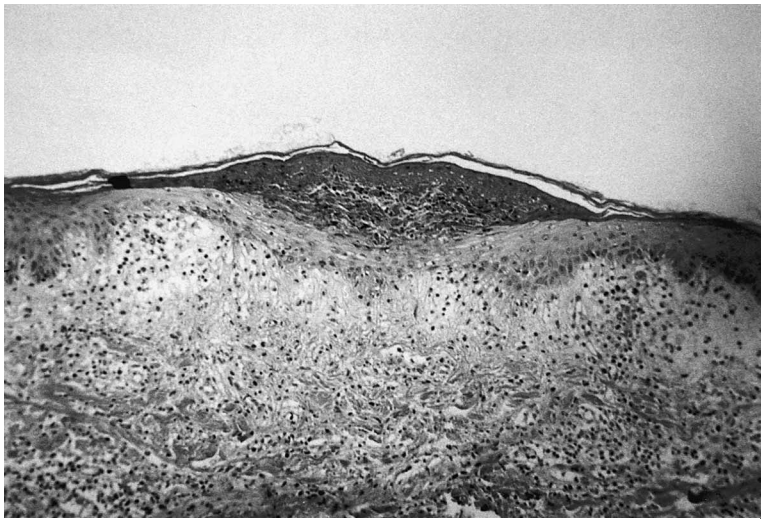

Fig. 3 Histopathology of the bitten site of Case 1 patient. At the center, necrotic ulcer was found with leaked erythrocytes inside. In the upper layer of the corium, infiltrating neutrophils and mildly thickened vascular walls with moderately edematous changes were observed.

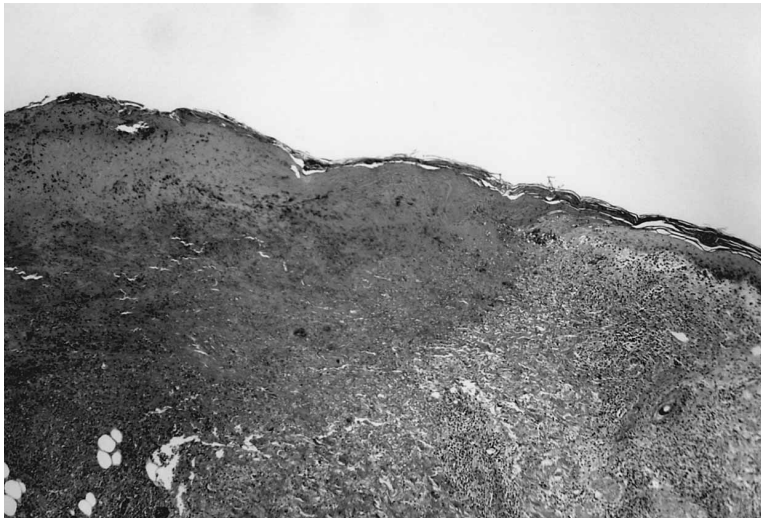

Fig. 4 Histopathology of erythemas on the back of Case 1 patient. Note the blisters under the epidermis and monocytic cell infiltration in the upper layer of the corium.

formed at the bitten site on the right femoral region and at the generalized edematous erythemas. The biopsy of the bitten site showed a necrotic ulcer at the center with leaked erythrocytes inside. Neutrophil infiltration and mild thickening of the vascular walls with a moderate edematous change were also observed in the upper layer of the epidermis (Fig. 3). The biopsy of the generalized edematous erythemas showed blisters under the epidermis and monocytic cell infiltration in the upper layer of the epidermis, suggesting that the erythema was exudative (Fig. 4). Results of these biopsies were consistent with the pathological characteristics of tsutsugamushi disease.

Treatment and clinical course: Minocycline hydrochloride at 200 mg/day was started on

Table 1 Antibodies to tsutsugamushi disease agents. Serum samples obtained in the acute (onset) and recovery (14 days after the onset) phases were evaluated for antibodies to the strains of *Rickettsia tsutsugamushi* and Japanese erythematous fever. The IgM and IgG antibodies to Kawasaki strain were significantly increased in Case 1 patient.

Case	Phase	Strains of tsutsugamushi rickettsia (IIF)										Japanese erythematous fever		PCR for tsutsugamushi rickettsia
		Gilliam		Karp		Kato		Kawasaki		Kuroki				
		1gM	1gG	1gM	1gG	1gM	1gG	1gM	1gG	1gM	1gG	1gM	1gG	
Case 1	Acute	＜10	←	←	←	←	←	←	←	＜10	←	(−)	←	(−)
	Recovery	40	＜10	←	←	←	←	80	160	＜10	←	(−)	←	(−)
Case 2	Acute	＜10	←	←	←	←	←	←	←	＜10	←	(−)	←	(−)
	Recovery	160	≧320	＜10	160	＜10	160	≧320	≧320	＜10	80	(−)	←	(+)

Table 2 Incidences of tsutsugamushi disease in Kanagawa Prefecture in 1998. Increasing incidence was noted for Hadano City.

No.	Sex	Age	Admission time	Infection time (presumed)	Infection place (presumed)	Activity type
1	F	74	10/26	unknown	Hadano-city	gardening
2	M	92	10/20	unknown	unknown	unknown
3	F	49	10/28	10/20	Yamakita-town	mashroom picking
4	F	48	11/3	11/1	Matsuda-town	golf
5	F	54	11/6	11/2	Hadano-city	walking
6	M	55	11/25	116	Ohi-town	yam
7	M	61	10/23	10/10	Yamakita-town	farming
8	F	72	11/1	10/31	Hadano-city	gardening
9	F	62	10/15	10/15	Hadano-city	others
10	M	62	11/8	10/30	South ashigara-city	yam
11	F	56	11/7	11/1	South ashigara-city	farming
12	M	41	11/9	11/4	Yamakita-town	gardening
13	F	53	11/11	11/early	South ashigara-city	farming
14	M	69	11/10	11/10	South ashigara-city	mountain working
15	M	33	11/15	10/late	South ashigara-city	others
16	F	68	unknown	11/18	Yamakita-town	farming
17	F	73	11/30	11/24	Yamakita-town	farming
18	M	64	unknown	12/4	South ashigara-city	mountain working
19	M	52	12/3	11/late	South ashigara-city	others
20	F	55	12/20	12/16	Ohi-town	farming

admission. The fever resolved in a few hours, and the eruption disappeared in 5 days.

Case 2: Female, 54 years old.
Chief complaint: Generalized eruption.
First visiting date. November, 12, 1998.
Familial and past histories: None special.
Present history: She found an induration with a diameter of 1cm with flare at the right flank after she walked her dog on November 3, 1998, in Matsuda City,

Kanagawa Prefecture. Fever of about 38℃ developed on November 16, 1998. Since edematous erythemas developed on the whole body, she consulted a nearby practitioner and was referred to our department for a closer examination and treatment.

Clinical findings: A 10 × 15 mm black crust with a red induration was found on the right trunk. Diffuse, undefined edematous erythemas were noted on the whole body including the face. The right axillary lymph node was palpable.

Laboratory findings: General hematological examination including differential white blood cell count showed no abnormality. Blood biochemistry showed that the hepatic function was normal as indicated by GOT of 30 U/l and GPT of 28 U/l. CRP was high at 1.42 mg/dl. Although erythrocyte sedimentation rate was high at 65 mm/h, coagulability was not markedly prolonged with APTT of 39.5 sec, PT of 13.5 sec, fibrinogen of 535 mg/dl, and FDP of 101 μg/dl.

Treatment and clinical course: With a diagnosis of tsutsugamushi disease, minocycline hydrochloride at 200 mg/day was started on admission. The fever resolved in 10 hours, and the eruption disappeared in 5 days.

RESULT

In the present cases, serum samples were obtained in the acute (onset) and recovery (14 days after the onset) phases and examined for antibody to tsutsugamushi disease agents and Japanease erythematous fever by indirect immunofluorescence (IIF).

Polymerase chain reaction (PCR) for tsutsugamushi rickettsia was performed on skin biopsy samples.

The results summarized in Table 1 show that both cases were negative for Japanese erythematous fever antibody. In Case 1, both IgM and IgG antibodies increased significantly only for Kawasaki strain, while PCR analysis was negative for tsutsugamushi rickettsia, Thus, because of the clinical symptoms and the marked increase in tsutsugamushi antibody. Case 1 was diagnosed to be a case of the new type tsutsugamushi disease by Kawasaki strain. In Case 2 PCR was positive for tsutsugamushi rickettsia, and both IgM and IgG antibodies increased significantly for Kawasaki and Gilliam strains. Therefore, Case 2 was diagnosed to be tsutsugamushi disease, while the responsible strain was not identified. We speculate that IIF detected antibodies to the antigen(s) common to these strains [8]. It is generally thought that tsutsugamushi disease agents can be found in the crust, however, PCR analysis performed on the tissue samples of Case 1 patient did not identify the agent. This negative result was likely due to the fact that the skin samples were fixed with formalin or the crust samples contained less than two copies of rickettsia DNA required for PCR detection [9].

DISCUSSION

In tsutsugamushi disease, an eruption develops first at the bitten site. The eruption begins to show flare and blisters 3 to 5 days later and then turns to a black crust with a red induration. By 12 to 14 days after infection, generalized diffuse eruptions, i.e., edematous erythema, without itch develop and last for 7 to 10 days. Systemic symptoms of the disease include fever of about 40℃ and swelling of associated lymph nodes, both of which appear by about 10 days of infection [1, 4, 10]. It has been reported that nearly 30% of the patients with tsutsugamushi disease may die of DIC unless appropriately treated [4].

In the 10-year period between 1987 and 1996, a total of 456 patients with tsutsugamushi disease were reported in Kanagawa Prefecture, Japan. All these cases occurred in November. Incidence is more frequent in counties than cities. Among the counties, Yamakita Town of Ashigarakami County has been noted for the highest incidence for this 10-year period, with 246 cases (53.9% of the total) occurring in this county. Among the cities, Minami-Ashigara City had the highest incidence, with 64 cases (14.0% of the total). Because Yamakita Town and Minami-Ashigara City border to each other, the area of potential incidence is rather limited. It was also found that the incidence of tsutsugamushi disease was significantly more frequent in males of 50 years of age or older who worked in the flat farmlands [11].

In Japan, approximately 1,000 cases of tsutsugamushi disease were reported every year, and of those, about 46 cases occurred in Kanagawa Prefecture [11, 12, 13]. In 1998, there were 20 cases in Kanagawa Prefecture. In this year, most of these 20 cases suffered the new type tsutsugamushi

disease by Kawasaki strain. One of the present two cases was also attributed to Kawasaki strain. Since 1984, Kawasaki, Kuroki, and Karp strains have accounted for approximately 60%, 20%, and 20%, respectively, of the cases. A significant increase in cases with Kawasaki strain also continued in 1998 [11]. No predominance was associated with sex or age. Similar to the previous years, the disease developed most frequently in November, with 8 of 20 cases occurring in this month, and a majority of the patients contracted the disease during working in the farm (Table 2). The incidences were equally distributed in the western part of Kanagawa Prefecture; 7 patients (35%) in Minami-Ashigara City, 5 patients (25%) in Yamakita Town, and 4 patients (20%) in Hadano City. Since in Hadano City, located near Mt. Fuji, only 40 cases (8.7% of the total incidence in Kanagawa Prefecture) had been reported in the previous 10 years [11, 13], 1998 was the year of the highest incidence for this city. Case 1 and 2 were both infected in Matsuda City located between Yamakita Town and Hadano City, the two areas that had not been considered a high incidence area. These findings suggest that the incidence of tsutsugamushi disease in Kanagawa Prefecture is spreading eastward along the Tomei Highway towards city areas and, consequently, the incidence is no longer rare in open fields. Development of traffic networks, the recent boom of outdoor activities, and the extension of residential and business areas into the forest areas may have played certain roles in the increasing incidence of tsutsugamushi disease. We conclude that tsutsugamushi disease can occur in any areas and, therefore, patients with skin eruption in association with fever should be attended with care.

ACKNOWLEDGMENT

We thank Dr. Hisashi Harada at the Hadano Health Center and Dr. Yumiko Furuya at the Kanagawa Hygiene Health Center for cooperation in performing the serological diagnosis.

The summary of this report was presented at the 744th Tokyo Regional Conference of the Japanese Association of Dermatology in 1999.

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