

## Three Cases of Tsutsugamushi Disease successfully treated with Clarithromycin.

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Three cases of tsutsugamushi disease were successfully treated with clarithromycin, a new macrolide antibiotic. This is the first report describing tsutsugamushi disease in Hirado area and the clinical application of clarithromycin to this rickettsial disease.

### Introduction

Tsutsugamushi disease had been considered to be an endemic disease occurring in summer along the large riversides of three northern prefectures in Japan; Akita, Yamagata, and Niigata prefectures. But from autumn through winter in 1946 and 1948, a new type of tsutsugamushi disease broke out in the Izu archipelago and in the east hillside of Mt. Fuji. This endemic outbreak prompted the formation of the regional rickettsiosis research group in 1954 and they conducted nation wide surveys which revealed the presence of several new types of tsutsugamushi disease. Thereafter increasing number of the cases of tsutsugamushi disease have been reported from many regions of Japan (1). But so far there has been no report on tsutsugamushi disease from Hirado, the northern island of Nagasaki prefecture in Japan. We report here three cases of tsutsugamushi disease successfully treated with clarithromycin, a new macrolide antibiotic.

### Case 1

A 49-year-old farmer was admitted to our hospital for headache and skin rash on December 24, 1992. In early December he went to nearby hills and from the middle of the month he noticed headache, chill, and fever with eruptions gradually spread all over the body. On admission, the body temperature 38.6°C, and physical examination revealed swelling of the lymph nodes in the cervical and bilateral inguinal region. And the erythematous papular eruptions were observed mainly on the trunk. An eschar was noted on the upper portion of the right internal malleolus and it was presumed to be the location of the

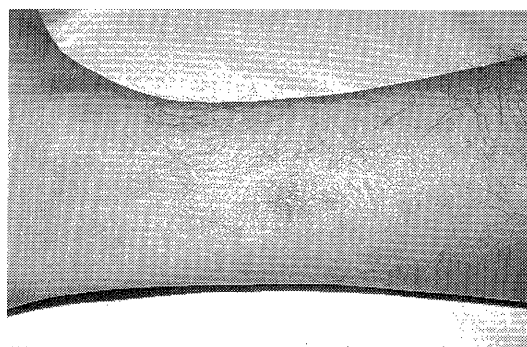


Fig. 1 An eschar was found on the right upper portion of internal malleolus.

Table 1. Laboratory data on admission

Peripheral blood		Biochemistry		
RBC	569X10 <sup>4</sup> /mm <sup>3</sup>	Bil	0.86	mg/dl
Hb	17.9 g/dl	T.P.	7.4	g/dl
Ht	49.1%	ALP	414	IU/L
WBC	7700/mm <sup>3</sup>	GOT	68	IU/L
St	48%	GPT	70	IU/L
Seg	15%	LDH	791	IU/L
Eo	0%	BUM	11.4	mg/dl
Plts	15.6X10 <sup>4</sup> /mm <sup>3</sup>	Cr	1.1	mg/dl
ESR	42/74	Na	135	mEq/L
		K	3.9	mEq/L
		Cl	96	mEq/L
Urinalysis				
	protein (++)			
	sugar (-)	CRP	9.3 mg/dl	
	RBC 2-3/F	HBs-Ag	(-)	
	WBC 25-30/F			

bite by tsutsugamushi mite (Fig. 1). Laboratory data on admission are shown on Table 1. White blood cell count was 7700/mm<sup>3</sup> with 48% stab forms and 15% segmented forms of the neutrophils. C reactive protein was 9.3 mg/dl and erythrocyte sedimentation rate was elevated to 42 mm/h. GOT (68 IU/L), GPT (70 IU/L), and LDH (791 IU/L) were slightly elevated. The clinical course of the patient

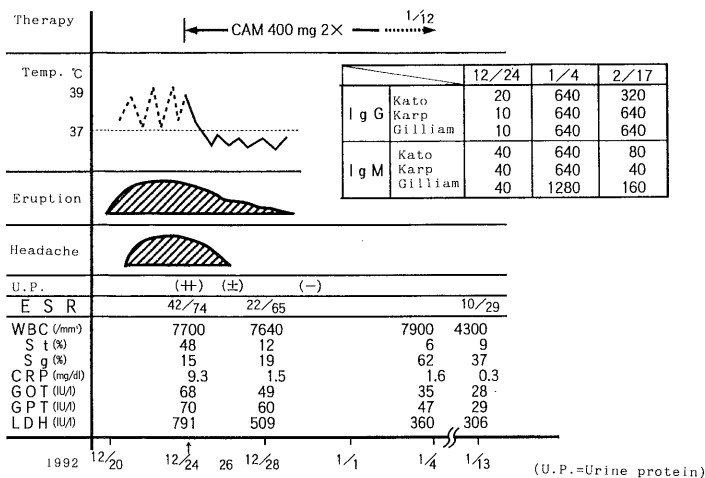


Fig. 2 Clinical course of case 1

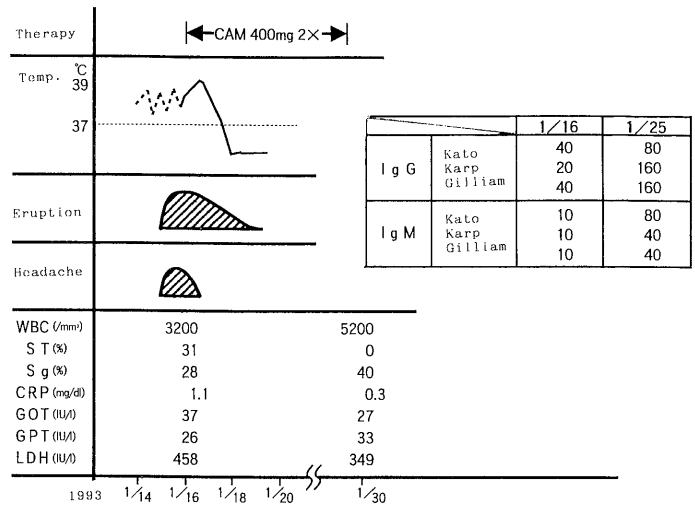


Fig. 3 Clinical course of case 2

Table 2. Laboratory data

Peripheral blood		Biochemistry	
RBC	554X10 <sup>6</sup> /mm <sup>3</sup>	Bil	0.6 mg/dl
Hb	17.3g/dl	T.P.	7.0 g/dl
Ht	48.5%	ALP	168 IU/L
WBC	3200/mm <sup>3</sup>	GOT	37 IU/L
St	31%	GPT	26 IU/L
Seg	28%	LDH	458 IU/L
Eo	0%	BUM	15.5 mg/dl
Plts	16.0X10 <sup>6</sup> /mm <sup>3</sup>	Cr	1.4 mg/dl
ESR	10/32	Na	136 mEq/L
		K	3.8 mEq/L
		Cl	99 mEq/L
Urinalysis		CRP	1.1 mg/dl
protein	(+)		
sugar	(-)		
RBC	0-1/F		
WBC	25-30/F		

is illustrated in Figure 2. Immediately after admission, he received oral administration of clarithromycin (CAM) 400 mg per day, and the fever rapidly resolved. The headache subsided in 2 days, the eruptions and the proteinuria noted on admission also gradually disappeared in several days. The antibody titer of IgG and IgM against *Rickettsia tsutsugamushi* in paired sera was diagnostic.

Case 2

A 18-year-old man visited our hospital complaining of eruption and fever on January 16, 1993. Early January of this year, the patient went to Kawachi-tohge after returning from Fukuoka City. He developed fever from January

14 and on the evening of the next day he also developed headache and eruption spread all over the body. His body temperature was 38.2°C. Physical examination demonstrated tonsilitis and eruption all over the body but location of the bite could not be identified. Laboratory data of this case are shown on Table 2. White blood cell count was 3200/mm<sup>3</sup> with 31% stab and 28% segmented neutrophils. C reactive protein was elevated to 1.1 mg/dl. The clinical course of the patient is illustrated in Figure 3. He received 400 mg of clarithromycin (CAM) per day, and the fever subsided. The eruptions disappeared in a few days and the headache disappeared almost in one day. More than fourfold rise in antibody titer of IgG and IgM against *R. tsutsugamushi* between paired sera was considered to be diagnostic.

Case 3

A 49-year-old housewife visited our hospital, complaining of chills and general fatigue on November 28, 1992. The patient went to nearby hills on November 15. On consulting day, her body temperature was 36.7°C and physical examination demonstrated neither eruptions nor locations of any bite. Laboratory data are shown on Table 3. White blood cell count was 4000/mm<sup>3</sup> with 0% stab and 62% segmented from neutrophils. C reactive protein was elevated to 1.7 mg/dl. GOT (50 IU/L), GPT (36 IU/L), and LDH (529 IU/L) were slightly elevated. The clinical course of the patient is illustrated in Figure 4. Because of the common cold-like symptoms, the patient received 750 mg/day of amoxicillin (AMPC) and mefenamic acid but the fever persisted. So the antibacterial drugs were changed to cefotiam hexetyl HCL (CTM-HE) on November 29. However, she still developed high fever and generalized eruptions on December 1. Considering the possibility of the

Table 3. Laboratory data

Peripheral blood		Biochemistry		
RBC	465X10 <sup>4</sup> /mm <sup>3</sup>	Bil	0.42	mg/dl
Hb	11.0g/dl	T.P.	7.6	g/dl
Ht	34.2%	ALP	142	IU/L
WBC	4000/mm <sup>3</sup>	GOT	50	IU/L
St	0%	GPT	36	IU/L
Seg	62%	LDH	529	IU/L
Eo	0%	BUM	12.9	mg/dl
Plts	18.7X10 <sup>4</sup> /mm <sup>3</sup>	Cr	0.9	mg/dl
ESR	N.D.	Na	139	mEq/L
		K	4.2	mEq/L
		Cl	102	mEq/L
Urinalysis		CRP	1.7	mg/dl
protein	(-)			
sugar	(-)			
RBC	25/30/F			
WBC	1/F			

drug rash and the ineffectiveness of these penicillin and cephem antibacterial drugs, 400 mg/day of clarithromycin (CAM) was started from December 2, and the fever rapidly subsided. The eruptions also disappeared three days after the administration of clarithromycin. On day 4 after the onset, white blood cell count was 4200/mm<sup>3</sup>; 42% stab and 23% segmented forms of neutrophils. C reactive protein was elevated to 7.7 mg, and the deterioration of the liver function was noticed with the value of GOT at 69 IU/L, GPT at 63 IU/L, and LDH at 824 IU/L. But in the mean time these values were normalized in three weeks. The elevation of antibody titer of IgG and IgM against *R. tsutsugamushi* in paired sera was diagnostic.

**Discussion**

Tsutsugamushi disease is an infectious disease caused by *Rickettsia tsutsugamushi* transmitted by the bite of larval tsutsugamushi mite. The transmission of *R. tsutsugamushi* to tsutsugamushi mite from generation to generation is by ovarian transmission. This is the reason why the outbreak of tsutsugamushi disease may become endemic but not truly epidemic (2). Reports of regional occurrence are therefore important in regional medical treatment. All three patients in this report went to nearby hills 1-2 weeks before onset. Although the high value of IgG titer in case 2, immediately after the onset, suggested an inapparent infection of tsutsugamushi disease (3). The patient's symptoms developed soon after he went to Kawachi-tohge, a resort area in Hirado. Therefore, other possibility of infection was hardly conceivable. Although an eschar is valuable for the diagnosis of tsutsugamushi disease, it was not identified in our case 2 and 3. Nakagawa et al also

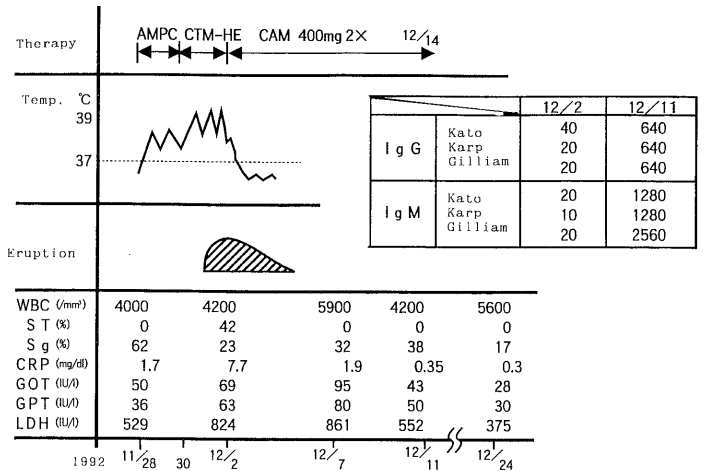


Fig. 4 Clinical course of case 3

reported a case of tsutsugamushi disease without eruption or eschar, and emphasized that one should be aware of tsutsugamushi disease without eschar (4). Traditionally tetracycline and its analogs or chloramphenicol have been considered to be the mainstay in treating tsutsugamushi disease (1). However, the adverse reactions often make it difficult to administrate these drugs particularly to pregnant women, children, and patients allergic to them. Macrolide antibiotics, on the other hand, are considered to be safe drugs due to more than 40 years clinical use, and erythromycin was already proved to have strong growth-inhibiting action against *R. tsutsugamushi* in vivo (5). But its clinical efficacy had been considered to be weak. Clarithromycin is one of the newly developed macrolide derivatives which is stable in gastric acid compared to conventional macrolide antibiotics and shows outstanding tissue transfer (6). Single oral administration of 200 mg clarithromycin reportedly yielded a maximum blood concentration of 1.16 µg/ml (7). In vitro drug susceptibility test, the MIC of clarithromycin against *Rickettsia rickettsii*, *R. conorii*, and *R. israeli* was at 1-2 µg/ml, several times higher than that of erythromycin (8), but there are no report on the clinical application of this antibiotic to tsutsugamushi disease as far as we know. In these three reported cases here, the effect of clarithromycin was almost comparable to that of minomycin whose effect is already shown in clinical trials (9). This is the first report, to our knowledge, on the effectiveness of clarithromycin in the cases with tsutsugamushi disease. We believe that the clinical application of this new macrolide antibiotic in this disease should be further studied.

## References

- 1) Yamasaku F. Tsutsugamushi disease. *Nihon Ishikai zasshi* (The Journal of the Japan Medical Association) 103 : 1810, 1990 (in Japanese).
- 2) Takada N, Fujita H. Social and epidemiological considerations concerning the causes for the rapid spread of tsutsugamushi disease. *Koshu Eisei* (Hygiene) 52 : 555, 1988 (in Japanese).
- 3) Suzuki H. Epidemiology of tsutsugamushi disease. *Kagaku Ryouhou No Ryouiki* 3 : 32, 1987 (in Japanese).
- 4) Nakagawa Y, Huruie H, Satou H, Matsumoto Y. A case of severe tsutsugamushi disease without eruption. *Nihon Kansenshogakkai zasshi* (The Journal of The Japanese association for Infectious Disease) 68 : 1433, 1994 (in Japanese with English abstract).
- 5) Miyamura S, Sato N, Tamura A. In Vitro Susceptibility of recent clinical isolate of *Rickettsia tsutsugamushi* to chemotherapeutic agents. *Nihon Kansenshogakkai Zasshi* (The Journal of The Japanese Association for Infectious Disease) 59 : 486, 1985 (in Japanese with English abstract).
- 6) New Drug symposium TE-031, 35th General Meeting of the Japanese Society of Chemotherapy, Morioka, 1987.
- 7) Suwa T, Urano H, Kodama T, Nakamura M, Watanabe T. Biokinetics of TE-031 (report No.8). *Chemotherapy*, 36 : 921, 1988 (in Japanese).
- 8) Maurin M, Raoult D. In vitro susceptibilities of spotted fever group *Rickettsiae* and *Coxiella burnetii* to clarithromycin. *Antimicrob. Agents Chemother* 37 : 2633, 1994.
- 9) Watanabe K, Kohno S, Hara K, et al. Clinical and serological study of Tsutsugamushi disease. *Chemotherapy* 36 : 954, 1988 (in Japanese with English abstract).