



# Conjunctival Injection, Episcleral Vessel Dilation, and Subconjunctival Hemorrhage in Patients with New Tsutsugamushi Disease

Tsuyoshi Kato,\*<sup>‡</sup> Kazuhiko Watanabe,\*<sup>‡</sup> Michiko Katori,<sup>†</sup>  
Yasuhito Terada<sup>†</sup> and Seiji Hayasaka<sup>‡</sup>

Departments of \*Ophthalmology and <sup>†</sup>Internal Medicine, Asahi General Hospital;  
<sup>‡</sup>Department of Ophthalmology, Toyama Medical and Pharmaceutical University, Japan

**Abstract:** Tsutsugamushi disease is found in two types: classical and new. There have been very few reports describing the ocular findings in patients with the new form. We have described four patients with this type, selected according to their clinical and laboratory findings, including immunofluorescent titers and polymerase chain reaction results. Eyes were examined by standard ophthalmic procedures. Patient 1 had bilateral conjunctival injection and subconjunctival hemorrhage; patients 2–4 had conjunctival injection and episcleral vessel dilation bilaterally. We believe that conjunctival injection is found in most eyes of patients with new tsutsugamushi disease. **Jpn J Ophthalmol 1997;41:196–199** © 1997 Japanese Ophthalmological Society

**Key Words:** Conjunctival injection, new tsutsugamushi disease, rickettsia.

## Introduction

Tsutsugamushi disease and scrub typhus are mite-borne rickettsioses caused by *Rickettsia tsutsugamushi* or *R. orientalis*, and are characterized by fever, rash, and lymphadenopathy<sup>1–4</sup> (Table 1). The name *tsutsugamushi disease* has been used in Japan for 150 years,<sup>3,4</sup> although the term *scrub typhus* was first used in the Asia-Pacific area during World War II.<sup>1</sup>

Tsutsugamushi disease has recently been recognized as occurring in two forms, according to carrier, epidemic area and season, and specific clinical signs and symptoms.<sup>3,4</sup> The classical type is carried by *Leptotrombidium akamushi* and found in the river areas of Niigata, Yamagata, and Akita Prefectures in the summer. The new type is carried by *L. pallidum* and *L. scutellaris* and occurs sporadically throughout Japan in spring and autumn. Ocular findings of patients with the classical form, including conjunctival

injection and iridocyclitis, have long been reported,<sup>3–6</sup> but we know of only a few reports describing patients with the new form although the incidence of the new form has been increasing since 1975.<sup>3</sup> This study describes the ophthalmologic characteristics of four patients with new tsutsugamushi disease.

## Patients and Methods

We examined four patients who had the new form of tsutsugamushi disease. In direct immunofluorescent titers of the Kato, Karp, and Gilliam strains of *R. tsutsugamushi* were determined, and polymerase chain reaction was used to confirm the carrier according to the procedure described by Morita and associates.<sup>7</sup>

## Case Reports

Clinical and laboratory data are shown in Tables 2 and 3.

### Patient 1

A 25-year-old man from Nyuzen, Toyama Prefecture, worked outdoors on November 10, 1992. On November 20, he complained of fever and a macular

Received: June 17, 1996

Address correspondence and reprint requests to: Tsuyoshi KATO, MD, Department of Ophthalmology, Toyama Medical and Pharmaceutical University, 2630 Sugitani, Toyama 930-01, Japan

**Table 1.** Mite-Borne Rickettsioses Caused by *Rickettsia tsutsugamushi*

	Tsutsugamushi Disease		
	Classical	New	Scrub Typhus
Recognized	150 years ago	1948	During World War II
Carrier <sup>a</sup>	<i>L. akamushi</i>	<i>L. pallidum</i> <i>L. scutellaris</i>	<i>L. deliensis</i>
Epidemic area	River areas of Niigata, Yamagata, and Akita Prefectures	Sporadically, throughout Japan	Southeast Asia, India, Australia, China
Months	June, July, August, September	May, October, November, December	All year
Incubation period (days)	5-14	5-21	10-12
Signs and symptoms			
Insect bite	+	+	±
Fever	+	+	+
Rash	+	++	+
Lymphadenopathy	+	±	++
Conjunctival injection	+	+	+
Iridocyclitis	+	-	-
Retinal hemorrhage	-	-	+
Prognosis	Poor <sup>b</sup>	Fair	Fair

+ = present, ± = sometimes present, ++ = marked, - = absent.

<sup>a</sup>Leptotrombidium.

<sup>b</sup>Before antibiotics.

rash on the face and trunk. A lesion covered by a black scab was found on his left lower leg. Ophthalmic examination on November 28 found good bilateral visual acuity (1.0) and intraocular pressures of 12 mm Hg. There was conjunctival injection and subconjunctival hemorrhage in both eyes (Figure 1), which otherwise appeared normal. Serology results showed elevated titers of the Kato, Karp, and Gilliam strains of *R. tsutsugamushi*. The Gilliam strain was particularly high 19 days after onset. Treatment included intravenous minocycline, 200 mg/day for 7 days, followed by oral minocycline, 100 mg/day for 5 days. Topical pranopfen, 0.1% was instilled four times daily. Clinical signs and symptoms improved 7 days after treatment began and had disappeared 12 days later.

### Patient 2

A 40-year-old woman from Asahi, Toyama Prefecture, worked in a field on May 8, 1995. On May 15, she complained of fever, chills, headache, and lymphadenopathy. An insect bite was found at the left axilla. The patient was referred to our hospital on May 22. Ophthalmic examination on May 23 found good corrected bilateral visual acuity (0.9) and intraocular pressures of 13 mm Hg. Conjunctival injection and episcleral vessel dilation were present in both eyes, which otherwise appeared normal (Figure 2). Serology testing found no elevated titers for any strains of *R. tsutsugamushi*, but polymerase chain reaction analysis identified the organism's DNA in the patient's blood. Treatment included intravenous minocycline, 200 mg/day for 8 days, and topical instilla-

**Table 2.** Clinical Data

Patient Number	Age (year)	Sex	Residency <sup>a</sup>	Month of Onset	Clinical Signs and Symptoms				
					Insect Bite	Fever (°C)	Rash	Lymphadenopathy	Conjunctival Injection
1	25	M	Nyuzen	November	+	40	+	-	+
2	40	F	Asahi	May	+	38	+	+	+
3	67	F	Asahi	May	+	39	+	+	+
4	77	F	Asahi	May	+	39	+	-	+

+ = present, - = absent.

<sup>a</sup>Toyama Prefecture

**Table 3.** Laboratory Data

Patient Number	Days After Onset	Indirect Immunofluorescent Titers			Polymerase Chain Reaction
		Kato	Karp	Gilliam	
1	10	1:640	1:320	1:640	Present in blood Present in blood and cerebrospinal fluid
	19	1:320	1:160	1:2560	
2	10	1:<10	1:<10	1:<10	
3	9	1:1280	1:1280	1:640	
	19	1:2560	1:2560	1:1280	
4	2	1:80	1:40	1:80	
	14	1:80	1:160	1:320	

tion of 1% minocycline four times daily. Clinical signs and symptoms improved 7 days after treatment began.

#### Patient 3

A 67-year-old woman also from Asahi in Toyama Prefecture, worked in a field on May 6, 1995. On May 13, she complained of fever, general fatigue, and macular rashes. She was referred to our hospital on May 22; lymphadenopathy and an insect bite on her left lower leg were found. Ophthalmic examination on May 23 found poor visual acuity bilaterally (0.2 OD, 0.1 OS) with intraocular pressures of 12 mm Hg. There was bilateral conjunctival injection and episcleral vessel dilation. Corneas and anterior chambers appeared clear, but lens opacities occluded views of both fundi. Ultrasonography and electroretinography found no abnormalities. Serology testing disclosed elevated *R tsutsugamushi* titers. Kato and Karp strain titers were particularly elevated 19 days after onset of symptoms. Polymerase chain reaction analysis identified *R tsutsugamushi* DNA in her blood and cerebrospinal fluid. Treatment included intravenous minocycline, 200 mg/day

for 8 days, and topical instillation of 1% minocycline four times daily. Clinical signs and symptoms improved 7 days after treatment began.

#### Patient 4

A 77-year-old woman from the same town as patients 2 and 3 complained of fever and rash on May 24, 1995. The patient denied having been in a field or wooded area, however, an insect bite was found on her right upper back. Ophthalmic examination on May 26 found bilateral conjunctival injection and episcleral vessel dilation. Bilateral corrected visual acuity was 0.6 and intraocular pressures were 11 mm Hg. Cortical opacities were present in both lenses; fundi appeared normal except for bilateral drusen. Serology testing found elevated *R tsutsugamushi* titers. Treatment included intravenous minocycline, 200 mg/day for 10 days, and topical instillation of 1% minocycline four times daily. Clinical signs and symptoms improved 7 days after start of treatment.

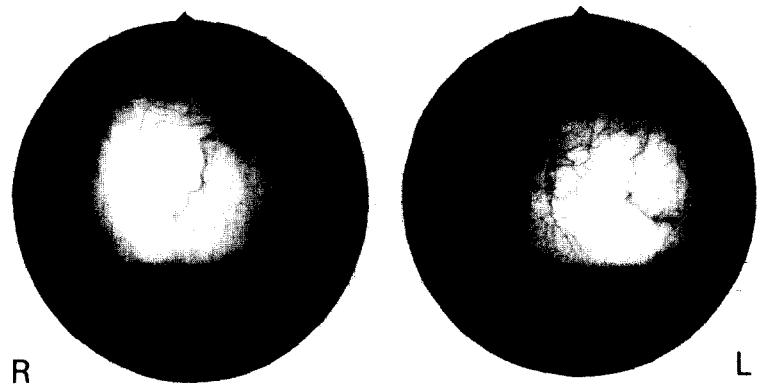
### Discussion

The four patients described in the present study all had fever, rashes, and insect bits; patients 2 and 3



**Figure 1.** Patient 1: Bilateral conjunctival injection and subconjunctival hemorrhage.

**Figure 2.** Patient 2: Bilateral conjunctival injection and episcleral vessel dilation.



also had lymphadenopathy. These are all typical clinical findings in tsutsugamushi disease.<sup>3,4</sup> Patients 1, 3, and 4 had elevated *R tsutsugamushi* titers; in patients 2 and 3, the DNA of this carrier was identified by polymerase chain reaction analysis confirming the diagnosis as tsutsugamushi disease. All four patients lived in Toyama Prefecture, and their acute febrile illness developed in November or May. In all four, the location and season were consistent with the new form of the disease,<sup>3,4</sup> although the carrier was not identified in each case.

Several ocular findings are associated with classical tsutsugamushi disease and scrub typhus including conjunctival injection and iridocyclitis,<sup>3-6</sup> whereas conjunctival injection, subconjunctival hemorrhage, dilation of the retinal vein, retinal edema, retinal hemorrhage, soft exudate, disc edema, and vitreous opacity were described in patients who had scrub typhus.<sup>2,8,9</sup> In the present study, our four patients with the new form of tsutsugamushi disease had only conjunctival injection, episcleral vessel dilation, and subconjunctival hemorrhage, suggesting that clinical manifestations of new tsutsugamushi disease may be milder than those of the classical form or scrub typhus. It is also possible that the different finding in the two types of tsutsugamushi disease and scrub typhus may be related to involvement of a variety of strains in *R tsutsugamushi* and the larvae of several *Leptotrombidium* species.<sup>3,4</sup> Yamasaku<sup>4</sup> reported that systemic vasculitis and perivasculitis with infiltration of lymphocytes and plasma cells are found histopathologically in tsutsugamushi disease. Therefore, it is reasonable to believe that the conjunctival injection, episcleral vessel dilation, and subconjunctival hemorrhage in our patients may result from infiltration of these cells, although histopathology studies were not done.

All four of our patients received immunofluorescent testing; patients 2 and 3 were further evaluated

by polymerase chain reaction analysis as described by Morita et al.<sup>7</sup> Tachibana<sup>3</sup> has recommended the intravenous therapy of minocycline or doxycycline at 200 mg/day for 7 days for treatment of tsutsugamushi disease; we used intravenous minocycline (200 mg/day for 7–10 days) for our patients, adding topical instillation of pranoprofen or minocycline. Efficacy of the various medication combinations could not be determined in the present study.

Ophthalmologists need to be aware that several ocular findings, including conjunctival injection, may occur not only in classical tsutsugamushi disease and scrub typhus but also in new tsutsugamushi disease.

---

We thank Dr. K. Kamimura at the Laboratory of Parasitology, Toyama Medical and Pharmaceutical University for his helpful advice.

---

## References

1. Brown GW. Recent studies of scrub typhus: A review. *J Roy Soc Med* 1978;71:507–10.
2. Paul SR, Karanth S, Dickson C. Scrub typhus along the Thai-Kampuchean border: New treatment regimen. *Tropical Doctor* 1987;17:104–7.
3. Tachibana N. Tsutsugamushi disease. *Jpn J Clin Med [Nippon Rinsho]* 1985;43:728–32.
4. Yamasaku F. Tsutsugamushi disease. In: Otani S, ed. *Handbook of internal medicine*. Vol 53B. Tokyo: Nakayama-Shoten, 1979: 251–53.
5. Kuwabara Y. Iridocyclitis in tsutsugamushi disease. *Jpn Rev Clin Ophthalmol* 1919;15:101–6.
6. Yoneyama T, Ibaraki M. An insect bite lesion of the eyelid in tsutsugamushi disease. *Jpn J Clin Ophthalmol* 1951;5:752–53.
7. Morita O, Ishikura M, Nambu A, Hashizume Y. Incidence of tsutsugamushi disease in Toyama Prefecture in 1993. *Ann Rep Toyama Inst Health* 1994;17:191–95.
8. Chamberlain WP Jr. Ocular findings in scrub typhus. *Arch Ophthalmol* 1952;48:313–21.
9. Scheie HG. Ocular changes associated with scrub typhus: A study of 451 patients. *Arch Ophthalmol* 1948;40:245–67.