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Case Report: Concurrent Sympatric Scrub Typhus and Japanese Spotted Fever in Japan

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Abstract. Scrub typhus and Japanese spotted fever—both rickettsial diseases—are endemic and notifiable in Japan and may cause a fatal outcome without prompt treatment. Here we present the first case of a concurrent sympatric infection of both diseases with grade II evidence. A 67-year-old woman, after a single event of potential exposure to the pathogens, presented with a 12-day history of fever, pharyngeal pain, papulo-erythematous rash, and pronounced fatigue. Her erythematous rash was distributed on her trunk and extremities, palms, and soles and eventually progressed to purpura. Fever persisted until doxycycline was administered on day 12. A significant > 4-fold increase in immunoglobulin G and immunoglobulin M titers against multiple serotypes of *Orientia tsutsugamushi* and *Rickettsia japonica* were revealed by indirect immunoperoxidase assays. These clinical and serological data, even in the absence of molecular or isolation evidence, provided grade II evidence that this was a concurrent infection of sympatric scrub typhus and Japanese spotted fever.

INTRODUCTION

Scrub typhus (ST) and Japanese spotted fever (JSF) are endemic and notifiable rickettsial diseases in Japan (Figure 1).[1] Approximately 400 ST and 200 JSF cases have been reported annually across the country, and the minimum incidence of JSF appeared to increase from 0.48/1,000,000 in 2005 to 1.69/1,000,000 in 2015, according to the National Epidemiological Surveillance of Infectious Diseases.[1] Trombiculid mites in their larval stage transmit *Orientia tsutsugamushi*, which in turn causes ST. Ixodid ticks transmit *Rickettsia japonica*, which in turn causes JSF. These diseases—both of which manifest with fever, general fatigue, painless and non-pruritic rash, and painless eschar—may cause a fatal outcome if appropriate treatment is delayed.[2,3] The estimated median case fatality rate of untreated ST, according to a systematic review, is 6.0%, although this value ranges widely from 0% to 70%,[2] very limited mortality data are available for JSF. In rural and mountainous areas, the habitat and behaviors of the vector may vary by season and geography; thus, there is the restriction of the population that are simultaneously exposed to those infections.[4] Scrub typhus is seen predominantly during spring in the Tohoku and Hokuriku areas, northeast Japan, whereas this disease is seen during autumn in the rest of Japan. Japanese spotted fever infections are seen from spring to autumn.[1,5]

Limitations in detecting rickettsemia by isolation and/or polymerase chain reaction (PCR), as well as serologically,[6] make early and accurate diagnosis challenging for both of these rickettsial diseases. Here we present the first case of a concurrent infection with ST and JSF, which was diagnosed serologically.

CASE DESCRIPTION

A 67-year-old female presented to a local doctor on September 25 with a 3-day history of chills, fever, pharyngeal pain, and general fatigue. She lived in the rural mountainous area of Chiba Prefecture, Central Japan (Figure 1). Before this illness, her daily activity had been entirely independent. She denied having observed any tick or mite bites, as well as undertaking any outdoor activities, apart from a bicycle accident, which had caused her to fall into bushes on the bank of a river, necessitating her to crawl to get out, a few days before the onset of the disease. She was referred immediately to the Kameda Medical Center because of her elevated lactate dehydrogenase plasma levels and thrombocytopenia. On physical examination, her body temperature was 39°C, her pulse was 92 beats/minutes, and her blood pressure was 119/74 mmHg. Her oxygen saturation was 98% in room air. She had inflamed pharynges, conjunctival bleeding, and a rice grain-sized papulo-erythematous rash with petechiae distributed bilaterally but asymmetrically on her trunk and extremities, palms, and soles. No eschars or lymphadenopathy were found. She was initially diagnosed with a viral infection and sent back home without medication. Significant thrombocytopenia, elevated myogenic enzymes, and elevated C-reactive protein were revealed by laboratory blood tests on day 3, and renal involvement was suggested by urine analysis (Table 1).

On September 29, 7 days after disease onset (day 7), because her fever had persisted and her family had noticed her inarticulate speech, she revisited the outpatient department. However, on physical examination and a brain computed tomography scan, no new objective abnormality was identified. She was again sent back home without any further medication. On October 4 (day 12), she returned because her fever persisted and the erythematous rash had progressed to purpura (Figure 2A), which also appeared on her palms and soles (Figure 2B). A consultant infectious disease doctor suspected a rickettsial infection. She was prescribed 100 mg doxycycline orally twice a day and was followed up in the outpatient department. The next day, her fever and other symptoms started to decline and subsided without any complications.

We performed indirect immunoperoxidase (IIP) assays, which demonstrated that among a panel of six serotypes of *O. tsutsugamushi*, on day 24 a significant increase in IgM titers against Irie/Kawasaki from < 40 to 1,280 and, to less extent,

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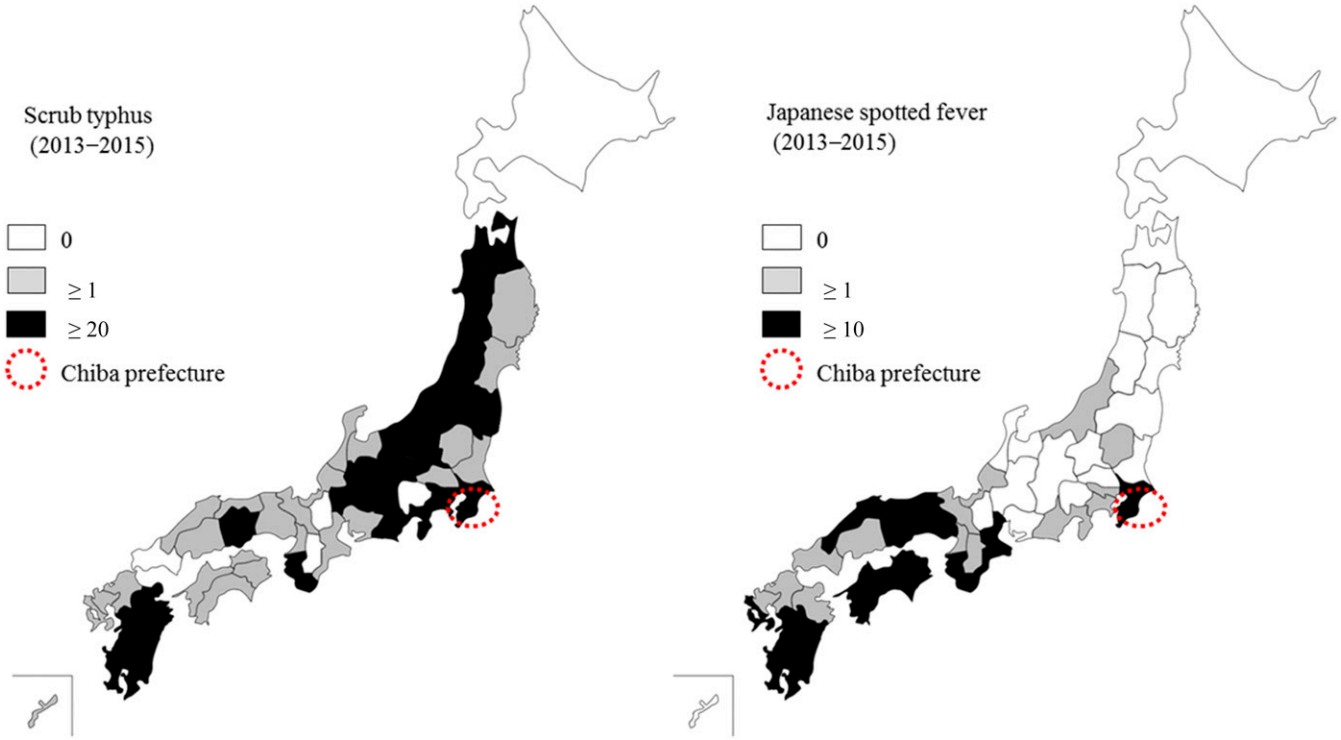

FIGURE 1. Distribution of scrub typhus and Japanese spotted fever (2013–2015). Data source: National Institute of Infectious Diseases Japan, Infectious Diseases Weekly Report. Available at: https://www.niid.go.jp/niid/en/survei/2085-idwr/ydata/6060-report-en2014.html. This figure appears in color at www.ajtmh.org.

Gilliam types were seen, whereas from day 3, the IgG titers against Irie/Kawasaki and Gilliam types were high (Table 2). On the contrary, a ≥ 4-fold increase against other types, including Kato, Karp, Hirano/Kuroki, and Shimokoshi, but without any IgM response, was seen in the follow-up IgG titers. A significant > 4-fold increase was seen in both IgM and IgG titers against *R. japonica*, with a rather blunted IgM response compared with the strong IgG dynamics. IgM against *Rickettsia typhi* was also elevated but without any IgG response. The indirect hemagglutination assay showed a compatible elevation of titers from < 40 (day 3) to 1,280 (day 12) and 2,560 (day 24) against *R. japonica*, but not against *R. typhi*. Taken together, these results are compatible with grade II evidence that the patient had contracted not only *O. tsutsugamushi* but also *R. japonica*.[7] Because we could not retrospectively obtain whole blood or buffy coat, we tested PCR for detecting *R. japonica* and *O. tsutsugamushi* using patient's serum on day 3, we only had a negative result.

TABLE 1
Laboratory data. Laboratory blood and urine tests on day 3

Item	Value	Unit	Reference value
WBC	3,700	μL	3,500–9,800
Hb	12.2	g/dL	11.0–15.3
Platelet	115,000	μL	130,000–370,000
Total protein	7.3	g/dL	6.7–8.3
Albumin	3.6	g/dL	3.4–5.8
AST	88	IU/L	13–33
ALT	36	IU/L	8–42
LDH	474	IU/L	119–229
ALP	203	IU/L	115–360
γ-GT	13	IU/L	10–47
Total bilirubin	0.5	mg/dL	0.2–1.0
Creatinine kinase	1,374	IU/L	45–163
BUN	15	mg/dL	8–22
Creatinine	0.84	mg/dL	0.6–1.2
Sodium	137	mEq/L	135–147
Potassium	3.6	mEq/L	3.3–4.8
Chloride	103	mEq/L	98–108
Plasma glucose	103	mg/dL	70–110
C-reactive protein	8.02	mg/dL	0.01–0.4
IgG	1,977	mg/dL	680–1,620
Urine analysis			
Urine protein	3+	–	–
Urine occult blood	3+	–	–

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; Hb = hemoglobin; LDH = lactate dehydrogenase; WBC = white blood cells; γ-GT = gamma glutamyltransferase.

DISCUSSION

This is the first report of a concurrent infection with *O. tsutsugamushi* and *R. japonica* with grade II evidence. We have extensive experience of diagnosing hundreds of ST and JSF cases at two referral laboratories, but we have never previously observed cross-reactivity between *O. tsutsugamushi* and *R. japonica*, whereas it was commonly seen between *O. tsutsugamushi* serotypes.[8] Therefore, although we did not secure molecular or culture isolation evidence for the current case, we believe the demonstration of a simultaneous serological response to both, after a single episode of potential exposure, was compelling evidence for a concurrent infection of ST and JSF. The patient likely contracted the diseases in an area where mites (*Leptotrombidium scutellare* and *Leptotrombidium pallidum*) and ticks (*Haemaphysalis flava*, *Haemaphysalis longicornis*, and *Ixodes ovatus*) co-exist, and where ST and JSF have been previously reported.[9–12] Furthermore, September and October are the only months when both infections occurred in Chiba Prefecture. Previous reports on concurrent infection with

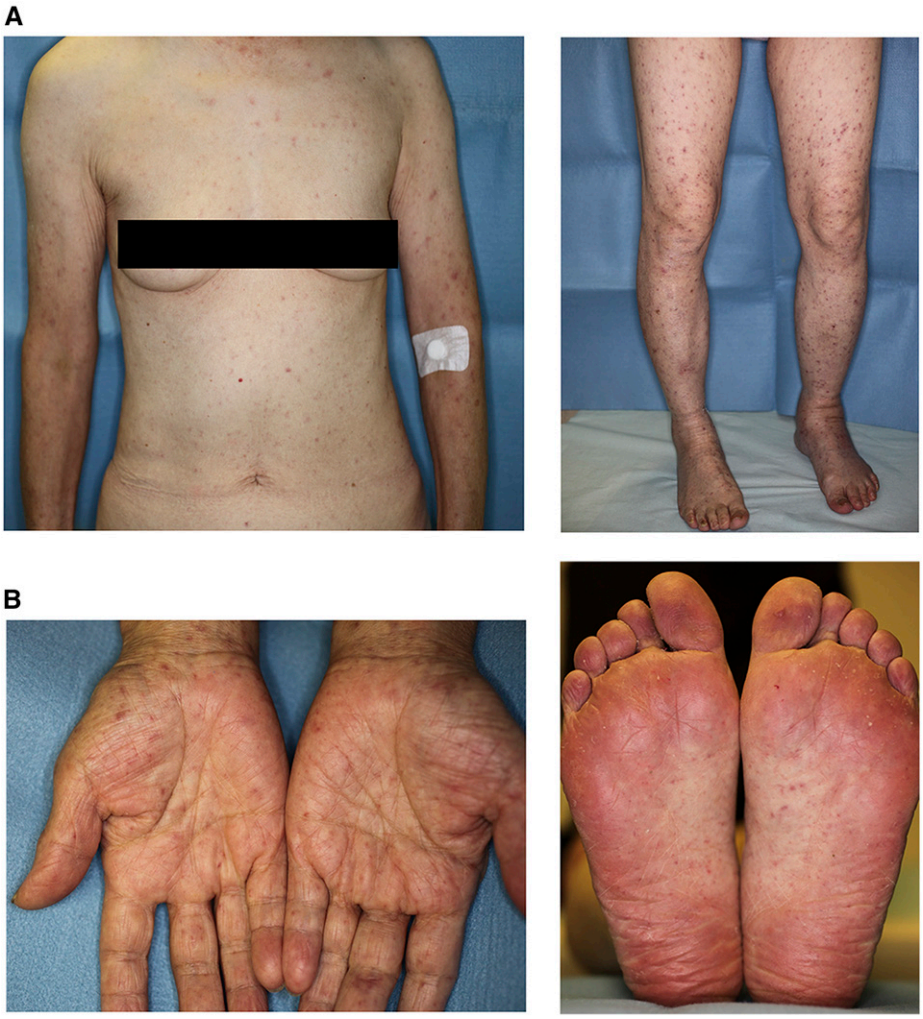

FIGURE 2. (**A**) Rash on trunk and extremities. An erythematous rash with purpura was present, predominantly on the extremities compared with the trunk. (**B**) Rash on palms and soles. A petechial rash on palms and soles. This figure appears in color at www.ajtmh.org.

rickettsial diseases have included, in China and Laos, *O. tsutsugamushi* with *R. typhi*.[7,13] The current case is important because—unlike *R. typhi*, which can cause a milder disease form, murine typhus—*R. japonica* may cause fatal JSF.

The patient initially presented with clinical features more typical of JSF; her erythematous rash with petechial and purpural lesions was distributed predominantly along the extremities and the torso, as well as the palms and soles.[14] We would have missed this concurrent infection had the patient been adequately treated on day 3 and had her recovery samples on day 24 not been tested. The eschar is one of the most common findings in ST and JSF, offering a valuable diagnostic clue,[15] but we did not detect it in this patient. The formation of an eschar, according to a nonhuman primate model, is reduced by preexisting cellular immunity in homologous infections.[16]

TABLE 2
Antibody titers measured by indirect immunoperoxidase assays

Methods	Day after the onset of symptoms		
	Day 3	Day 12	Day 24
Indirect immunoperoxidase assays	Reciprocal IgM/IgG titers; -, < 40		
O. tsutsugamushi			
Gilliam	–/640	–/1,280	160/1,280
Karp	–/160	–/1,280	–/1,280
Kato	–/80	–/80	–/320
Irie/Kawasaki	–/1,280	–/2,560	1,280/2,560
Hirano/Kuroki	–/80	–/640	–/1,280
Shimokoshi	–/80	–/2,560	–/1,280
R. japonica	–/–	40/640	160/2,560
R. typhi	–/–	160/–	320/–

The IgM/IgG titers of indirect immunoperoxidase assays against *Orientia tsutsugamushi* (six serotypes), *Rickettsia japonica*, and *Rickettsia typhi* on days 3, 12, and 24.

On day 3, significant IgG titers were already present against all *O. tsutsugamushi* serotypes tested—especially against the Irie/Kawasaki and Gilliam types. The subsequent dynamic increase of IgG titers, rising rapidly before any IgM response, strengthens the suspicion of previous exposure, with subsequent reactivation of a preexisting B-cell immune memory response. The strong rise in anti–*O. tsutsugamushi* Irie/Kawasaki type IgM antibodies—albeit a delayed and blunted response and with possible cross-reactivity against the Gilliam type in the analysis—is suggestive of active reexposure.[17] The early increase of IgG titers against the Karp and Shimokoshi types on day 12 was interpreted as cross-reactivity in conjunction with previous exposure. This atypical IgM antibody titer response indicates a reinfection of *O. tsutsugamushi* as previously described.[18] The IgG and IgM titers against *R. japonica* were, at first presentation, negative. However, the subsequent antibody response was characterized by an early, pronounced rise of the IgG titer, followed by a much

weaker and slower IgM titer increase. This finding is compatible with the characteristics of JSF serology in most cases of JSF from Japan.[19] The positive result from the hemagglutination assay for *R. japonica* on day 12 is noteworthy. The significant increase in anti-*R. typhi* IgM titer by IIP was not followed by a rise in the IgG titer, which remained negative throughout the time course. This finding, combined with the negative result in the *R. typhi* hemagglutination assay, is suggestive because of the presence of anti-*R. japonica* IgM antibodies, of cross-reactivity.

There is an urgent need for a better understanding of the antibody dynamics of rickettsial diseases in endemic areas with preexisting immunity and reexposure, complicated by the serotype diversity of *O. tsutsugamushi*. Had this patient been isolation positive and/or PCR positive for both pathogens, the case would have been unequivocally resolved on the basis of the proposed grading system.[7] However, previous findings in ST have shown that protective immunity results in a reduction of the bacterial load and a shorter bacteremic dissemination phase,[16] potentially limiting the likelihood of providing isolation-based and/or PCR-based evidence. The current case revealed the antibody dynamics to be even more complex in concurrent infections with JSF and emphasized the importance of more active screening for concurrent infection. In the present case, for example, if only IgM titers had been measured against *O. tsutsugamushi* and *R. japonica* on days 3 and 12, then the diagnosis would have been missed entirely (Table 2). Longitudinal studies would be beneficial, providing better insight into the dynamics of antibody responses in rickettsial illnesses.

CONSENT

A written consent signed by the patient was taken for the publication of this case report and any accompanying images, respectively.

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