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FIRST CASES OF SPOTTED FEVER GROUP RICKETTSIOSIS IN THAILAND

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Abstract. The first three cases of spotted fever group rickettsiosis from Thailand are reported. The patients presented with fever, headache, lymphadenopathy, and petechial maculopapular rash. One patient also had an eschar and overt evidence of confusion. An indirect fluorescent antibody test, an indirect immunoperoxidase test, and an enzyme-linked immunosorbent assay demonstrated a broad, strong reactions of the sera of the patients with spotted fever group rickettsia antigens of many species, but not with antigens of typhus or scrub typhus rickettsiae. All three patients responded to treatment with a single dose of doxycycline.

Spotted fever group (SFG) rickettsia that can cause disease in humans include *Rickettsia rickettsii* (Rocky Mountain spotted fever), *R. conorii*, (boutonneuse fever), *R. sibirica* (North Asian tick typhus), *R. australis* (Queensland tick typhus), *R. akari* (rickettsialpox), and *R. japonica* (Oriental spotted fever).[1,2] In Asia, *R. conorii* has been isolated from human cases of SFG rickettsiosis in India and Pakistan; *R. sibirica* in Russia, China, and Pakistan; *R. akari* in Korea; and *R. japonica* in Japan.[3] No case of SFG rickettsiosis has been reported from Thailand. We report three patients with serologic evidence of infection by an SFG rickettsia.

MATERIALS AND METHODS

All three patients were seen at Chiang Mai University Hospital, Chiang Mai (population 1,300,000) is one of the 76 provinces of Thailand. It is approximately 700 km north of Bangkok, the capital city and is subdivided into 22 districts. Muang district, the center of government administration, is also the site of the Faculty of Medicine at Chiang Mai University. Chiang Mai University Hospital, a 1,000-bed teaching hospital, serves as one of the primary cares facilities in Muang district as well as a referral center for Chiang Mai and neighboring provinces.

Weil-Felix tests were done using a microtiter technique[4] with commercial *Proteus* OX-2, OX-19, and OX-K antigens (Porton Cambridge, Newmarket, UK). Sera were tested for rickettsial antibodies using an indirect fluorescent antibody (IFA) test,[5] an indirect immunoperoxidase (IIP) test,[6] and an enzyme-linked immunosorbent assay (ELISA).[7,8] For the IFA, the SFG *Rickettsia* species used as antigens included cell culture propagated *R. rickettsii*, *R. conorii*, *R. sibirica*, *R. australis*, *R. akari*, TT-118 (Thai tick typhus), *R. montana*, *R. rhipicephali*, and *R. bellii*. *Rickettsia typhi* (Wilmington typhus group) and *R. tsutsugamushi* (Karp, Gilliam, Kato scrub typhus group) were used in a similar manner. Titers of sera were obtained at dilutions ranging from 1:50 to 1:102,400 using a fluorescence microscope (Zeiss, Oberkochen, Germany) and a 40× objective. The end point was defined as the highest dilution with discernible fluorescing organisms. Fluorescein-conjugated rabbit anti-human immunoglobulin (IgG) (heavy and light chain specific: Cappel Laboratories, Cochranville, PA) was used. The IIP test used previously published methods and *R. tsutsugamushi* (Karp, Gilliam, and Kato), *R. typhi*, and TT-118 antigens.[6] For the ELISA, *R. conorii* (SFG) and *R. prowazekii* (typhus group) antigens were used according to established procedures.[7,8] Horseradish peroxidase–labeled mouse anti-human IgG (Fc specific: Accurate Chemical and Scientific Corp., Westbury, NY) and goat anti-human IgM ([μ] chain specific: Kirkegaard and Perry, Gaithersburg, MD) were used as ELISA conjugates.

RESULTS

Case summary. Patient 1, a 47-year-old Thai man, was admitted on August 29, 1990 to

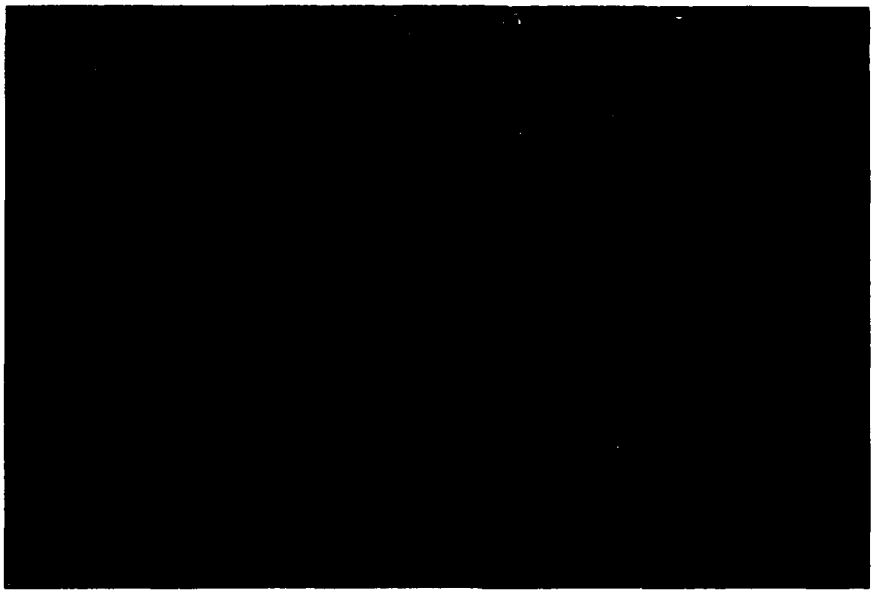

FIGURE 1. An eschar at the left infrascapular area of patient 1.

FIGURE 2. A petechial maculopapular rash on the palms of patient 2.

TABLE 1
*Results (titers) of the Weil-Felix test**

Patient	Date	OX-2	OX-19	OX-K
1	8/27/90	160	20	40
	8/30/90	320	Neg	20
	10/7/90	320	Neg	20
2	1/18/91	320	160	Neg
3	6/25/91	320	20	20
	7/17/91	320	40	40

* OX-2 = *Proteus* OX-2; OX-19 = *Proteus* OX-19; OX-K = *Proteus* OX-K; Neg = negative

Chiang Mai University Hospital because of a 10-day history of fever, headache, and myalgia. Three days prior to admission, he became confused and developed a maculopapular rash. The rash started on the back and then appeared on the anterior chest wall, abdomen, and extremities. The patient worked on a plantation near a forest and remembered having been bitten on his back by some kind of arthropod. Physical examination revealed normal body temperature, generalized lymphadenopathy, injected conjunctivae, and a generalized maculopapular rash that did not include the palms and soles. He was slightly confused. There was an eschar at the left infrascapular area (Figure 1). On the third day of hospitalization, petechiae appeared in the centers of the maculopapules. Laboratory findings included a hemoglobin level of 11.4 g/dl and a white blood cell (WBC) count of 14,200/mm^3 with 82% polymorphonuclear neutrophils (PMNs) and 18% lymphocytes. His platelet count was 169,000/mm.^{3} His chest radiograph was normal. He was given a single dose of 200 mg of doxycycline orally on the day of admission. His confusion improved within 48 hr of treatment.

Patient 2, a 12-year-old Thai boy, was admitted on January 18, 1991 to Chiang Mai University Hospital because of fever and myalgia of 10-days duration. On the fourth day of the fever, he developed a maculopapular rash that started on the face and was then noted on the body and extremities, including the palms and soles. Petechiae developed in the centers of the maculopapules. He lived near a forest but did not remember being bitten by a tick. Physical examination showed a body temperature of 40°C, cervical lymphadenopathy, and generalized petechial maculopapular rash (Figure 2). His hemoglobin level was 10.4 g/dl and he had a WBC count of 11,900/mm^3 with 85% PMNs,

TABLE 2
*Results (titers) of the indirect fluorescent antibody test**

Patient	Date	*Rickettsia rickettsii*	*R. conorii*	*R. sibirica*	*R. australis*	*R. akari*	TT-118	*R. montana*	*R. rhipicephali*	*R. helvetica*	RTW	*R. tsutsugamushi*
1	9/7/90	6,400	3,200	3,200	3,200	3,200	3,200	3,200	6,400	3,200	800	200
	9/19/90	3,200	12,800	12,800	3,200	12,800	12,800	3,200	6,400	3,200	400	400
2	1/21/91	100	400	200	200	200	400	100	100	100	<50	<50
	1/30/91	100	400	400	100	200	200	100	100	100	<50	<50
3	7/15/91	800	1,600	3,200	1,600	1,600	1,600	800	800	800	<50	<50

* TT-118 = Thai tick typhus; RTW = *R. typhi* Wilmington strain

TABLE 3
*Results (titers) of the indirect immunoperoxidase test**

Patient	Date	TT-118		*Rickettsia typhi*		*R. tsutsugamushi*	
		IgG	IgM	IgG	IgM	IgG	IgM
1	9/7/90	25,600	3,200	<50	<50	<50	<50
	9/19/90	51,200	6,400	<50	<50	<50	<50
2	1/21/91	3,200	800	<50	<50	<50	<50
	1/30/91	12,800	1,600	<50	<50	<50	<50
3	7/15/91	12,800	12,800	<50	<50	<50	<50

* TT-118 = Thai tick typhus

13% lymphocytes, and 2% monocytes. His platelet count was 242,000/mm.^{3} He was treated with a single dose of 100 mg of doxycycline orally and his fever resolved within 24 hr of treatment.

Patient 3, a 28-year-old Thai man, was admitted on June 24, 1991 to Chiang Mai University Hospital because of a four-day history of fever, headache, and myalgia. On the second day of the fever, he developed a maculopapular rash on the trunk and extremities that included the palms and soles. Petechiae appeared in the centers of the maculopapules. He denied having been bitten by a tick. Physical examination revealed a body temperature of 39.8°C, generalized lymphadenopathy, and generalized petechial maculopapular rash. His hemoglobin level was 16 g/dl and he had a WBC count of 11,000/mm^3 with 80% PMNs, 19% lymphocytes, and 1% eosinophils. His platelet count was 300,000/mm.^{3} His chest radiograph was normal. He was treated with 200 mg of doxycycline orally and his fever resolved within 48 hr of treatment.

Serologic study. All three patients had titers to *Proteus* OX-2 of 1:320 (Table 1). The IFA test showed antibodies against both the pathogenic and nonpathogenic species of the SFG rickettsia (Table 2), and the IIP test revealed clear antibody activity against TT-118, a member of this group of agents (Table 3). The ELISA showed activity against *R. conorii*, a representative SFG rickettsia used in the test. There was also some cross-reactivity against *R. prowazekii*, which belongs to the typhus group of organisms (Table 4).

TABLE 4
Results (titers) of the enzyme-linked immunosorbent assay

Patient	Date	*Rickettsia conorii*		*R. prowazekii*	
		IgG	IgM	IgG	IgM
1	9/7/90	>6,400	1,600	1,600	100
	9/19/90	>6,400	1,600	1,600	100
2	1/21/91	1,600	1,600	<100	<100
	1/30/91	400	1,600	<100	<100
3	7/15/91	>6,400	1,600	100	400

DISCUSSION

Although scrub typhus (*R. tsutsugamushi*) and murine typhus (*R. typhi*) are common diseases in Thailand,[9–14] SFG rickettsia have only been associated with arthropod infections. In 1962, an SFG rickettsia was isolated from a mixed pool of *Ixodes* and *Rhipicephalus* larval ticks collected in Chiang Mai, Thailand.[15] This isolate, subsequently designated TT-118 and commonly referred to as the Thai tick typhus agent, was found to be serologically distinct from other known SFG rickettsia.[16] The TT-118 isolate has usually been included in the panel of SFG rickettsia antigens used to serologically diagnose SFG rickettsiosis.[4]

The three cases of SFG rickettsiosis described in this paper are the first confirmed occurrence of this disease in Thailand. All three patients presented with fever, headache, lymphadenopathy, and petechial maculopapular rash, and one patient also had an eschar and was confused. These signs and symptoms are typical of SFG rickettsia infection,[1] and include confusion, which has been associated with multifocal rickettsial vascular infection of the brain in 28% of Rocky Mountain spotted fever patients.[3] All three Thai tick typhus patients responded to treatment with a single dose of doxycycline, a therapy known to be efficacious for treatment of scrub typhus[17] and used routinely in our hospital for that purpose.

In most hospitals in Thailand, including Chiang Mai University Hospital, the Weil-Felix

test is the only serologic test available for rickettsial diseases. In all three of our patients, the presence of *Proteus* OX-2 agglutinin alerted us to the possibility of the diagnosis of SFG rickettsiosis. Serum specimens were then subjected to more specific tests. *Proteus* OX-2 agglutinin has previously shown a sensitivity of only 47% in diagnosing Rocky Mountain spotted fever.[18] Its sensitivity in diagnosing other SFG rickettsioses is also probably low. Thus, the majority of cases of SFG rickettsiosis in Thailand may have been undiagnosed.

Rickettsial serology of the patients confirmed that they had been infected with an SFG rickettsia, but it could not specify which rickettsial species was involved. The IFA test, the IIP test, and the ELISA demonstrated broad, strong reactions of the sera with SFG rickettsia antigens of many species, but not with antigens of typhus or scrub typhus rickettsiae. Our patients could have been infected with *R. conorii, R. sibirica, R. australis, R. akari, R. japonica,* or a new SFG rickettsia. Further clinical, serologic, and field studies are needed to determine the incidence of the infection and to isolate the SFG rickettsia responsible for Thai tick typhus so that it might be propagated and characterized, with respect to the other SFG rickettsia, using modern genetic and biochemical techniques.

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