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Japanese Spotted Fever Involving the Central Nervous System: Two Case Reports and a Literature Review

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Japanese spotted fever (JSF), first reported in 1984, is a rickettsial disease caused by *Rickettsia japonica*. Until now, affliction of the central nervous system has been rarely reported. Here we report two cases of JSF associated with a central nervous system disorder such as meningoencephalitis.

CASE REPORTS

Case 1. A 58-year-old man mowed brushy vegetation on 15 August 1992. Eight days later, he developed a high fever and exanthemata on his upper extremities and trunk. He was admitted to a local hospital on 28 August 1992.

On admission he was afebrile. His extremities and trunk were covered with erythematous exanthemata, parts of which were petechial. His skin was also icteric. An eschar was detected on his left thigh. Neither lymphadenopathy nor hepatosplenomegaly was noted. His neck was stiff, and he was obtunded, with occasional mumbling, but otherwise his neurological examination showed no abnormalities.

Laboratory studies revealed leukocytosis, hepatic dysfunction, and bilirubinemia. His C-reactive protein (CRP) level was 6.3 mg/dl (versus a normal range of 0 to 0.5 mg/dl). Urinalysis showed bilirubinuria without hematuria and pyuria. Chest films and a computed tomography (CT) scan of the head were normal. His cerebrospinal fluid (CSF) contained 46 cells/mm^3, which consisted of 30 monocytes and 16 neutrophils/mm^3, 107 mg of sugar per dl, and 125 mg of protein per dl.

Intravenous administrations of various antibiotics including cefmetazole, clindamycin, aztreonam, and imipenem-cilastatin were ineffective. His CRP rose to a peak of 19.0 mg/dl. Since the exanthemata and eschar suggested rickettsial infection, 10 days after the onset of clinical symptoms, minocycline hydrochloride (MIN) at 400 mg/day was administered. He was then transferred to our hospital on 4 September 1992 due to his deteriorated consciousness and jaundice. Exanthemata and jaundice gradually resolved with continuous administration of MIN, and he regained consciousness. The CRP gradually decreased to 9.1 mg/dl. CSF evaluation on 8 September showed marked improvement. He was discharged without neurological deficits on 22 September, 5 weeks after the onset of symptoms.

Serological results enabled us to rule out scrub typhus, typhus, Lyme disease, and leptospirosis. Immunofluorescent studies 18 days later revealed greatly elevated levels of immunoglobulin G (IgG) and IgM antibodies to *Rickettsia japonica* (Table 1). These findings support our diagnosis of Japanese spotted fever (JSF).

Case 2. A 55-year-old man injured the lower portion of his left leg on a tree prickle at a bamboo plantation on 9 April 1998. The pain lasted for several days, and the wound closed gradually. Fourteen days after the incident, he developed a low-grade fever and sore throat. The next day, his body temperature rose above 40°C. He complained of headache and nausea, which were treated unsuccessfully with antibiotics and antipyretics. Rashes covered his anterior chest wall. His symptoms worsened, and he was admitted to a local hospital on 28 April disoriented and with shaking chills. The following day, the level of his consciousness further deteriorated, and he was referred to our hospital in a state of shock.

On arrival, his body temperature was 37.5°C, and his blood pressure 96/58 mmHg while receiving a continuous infusion of dopamine. Erythematous lesions with unclear margins, measuring 5 to 10 mm in diameter, were noted on his extremities and trunk. Some of the lesions were petechial, hemorrhagic, or fused. Neither lymphadenopathy nor hepatosplenomegaly was present. His neurological condition was poor: he was delirious, and his neck was stiff. He had bilateral papilledema, although his ocular movements and pupillary reflexes to light appeared to be normal. The muscle stretch reflexes were consistently hypoactive.

Laboratory studies revealed anemia, leukocytosis, and hepatic and renal dysfunction. A CT scan of the head revealed subdural hematoma over the left fronto-temporal lobe. An electroencephalogram showed diffusely slow activity (3 to 4 Hz).

He was in septic shock causing disseminated intravascular coagulation and multiorgan failure. He required intravenous catecholamine for his shock state, artificial ventilation for respiratory failure, and hemodialysis for acute renal failure. An empirical therapy of panipenem-betamipron, fluconazole, and acyclovir was administered intravenously.

On his 2nd and 3rd hospital days, he developed generalized convulsions. He also ran an intermittent fever, and the skin eruptions were worsening. We suspected that these prolonged symptoms were caused by rickettsial diseases, and intravenous MIN was administered on 10 May. He promptly became afebrile and more responsive. On 16 May, his 19th hospital day, artificial ventilation was disconnected. He showed remarkable

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TABLE 1. Titers of antibodies to *R. japonica, R. typhi, R. tsutsugamushi,* and *Proteus* strains

Patient no.	No. of days of illness	Ig class	*R. japonica*		*R. typhi*[b]	*R. tsutsugamushi*[c]			Weil-Felix test[d]		
			YH[a]	Aoki[b]	Wilmington	Gilium	Karp	Kato	OX2	OX19	OXK
1	13	IgM			40	<4	<4	<4	20	<10	<10
		IgG			40						
	18	IgM	320		40	<4	<4	<4	10	<10	<10
		IgG	1,280		40						
2	8	IgM	<10	40	<40	<4	<4	<4	<20	<20	<20
		IgG	20	40	<40						
	23	IgM	320	240	<40	<4	<4	<4	<20	80	<20
		IgG	5,120	>960	<40						

[a] Indirect immunofluorescence test.
[b] Indirect immunoperoxidase test.
[c] Complement fixation test.
[d] Latex agglutination.

clinical improvement, but retained retrograde memory disturbance. Paresthesia remained in the distal portion of his legs.

An indirect immunofluorescent assay in paired sera revealed elevated titers of antibody to *R. japonica*, but not to *Rickettsia tsutsugamushi* and *Rickettsia typhi*. Weil-Felix tests were negative (Table 1).

Reexamination of his CSF demonstrated pleocytosis with predominant lymphocytes and elevated protein levels (Table 2). An immunofluorescent assay of paired CSF specimens showed no increase in IgM antibody to *R. japonica*, but a 16-fold increase in IgG antibody (Table 2). Because of the clinical symptoms and effectiveness of MIN, we reached the final diagnosis of JSF.

TABLE 2. Diagnostic characteristics of CSF from patient 2

Characteristic	Characteristic (no. of days of illness) on study date			
	29 April (7)	19 May (27)	27 May (35)	12 June (51)
No. of leukocytes/mm^3	224	30	31	26
No. of lymphocytes/mm^3	144	30	31	22
No. of polymorphonuclear leukocytes/mm^3	80	0	0	4
Protein level (mg/dl)	116	133	58	27
Glucose level (mg/dl)	127	55	45	43
No. of erythrocytes/mm^3	12×10^4	193	0	0
R. japonica antibody titer[a]				
IgM	<10	<10	<10	
IgG	<10	160	160	

[a] Antibody titer against *R. japonica* strain YH by indirect immunofluorescent assay.

JSF is a recently recognized spotted fever group (SFG) rickettsial disease caused by *R. japonica*. JSF is transmitted to humans by various tick species infected with *R. japonica*. The triad of symptoms is fever, exanthema, and a tick bite eschar. The first known patient with JSF in Japan was reported as having SFG rickettsioses in 1984 (7). The causative agent of JSF was isolated from the serum of a patient in 1986 (14), was proven to represent a new type of SFG rickettsia (10, 15), and was named *R. japonica* (16).

The clinical characteristics of JSF are similar to those of scrub typhus. However, lymphadenopathy and hepatosplenomegaly are less common in JSF (6). The incubation period of JSF is about 7 days; the disease begins with an abrupt onset of a fever of 40°C or higher. Skin rashes tend to develop in the extremities and then spread to the trunk and entire body (6, 7), with some becoming petechial. The presence of exanthemata on the palms and soles is the symptom specific to JSF. The tick bite eschar in JSF patients is generally smaller than that in patients with scrub typhus. Clinically, JSF appears to be less severe than scrub typhus; however, complications may include disseminated intravascular coagulation, respiratory failure (4), or shock (3). Fatal cases have not yet been reported.

Of the five rickettsial diseases (typhus, spotted fever, scrub typhus, Q fever, and trench fever), the first three commonly cause central nervous system (CNS) infection (8). Table 3 shows the clinical features and laboratory findings of four patients with JSF with meningitis, including ours. JSF occasionally runs a severe course with CNS involvement, as described in our second case, and may be fatal. While only two patients with JSF suffered from obvious CNS involvement in the literature (2, 5), possible CNS involvement was suggested in several others, who had such symptoms as back stiffness (9) and a psychotic state with stupor (1).

In Japan, JSF tended to be endemic to areas of warm climate that border the Pacific Ocean. JSF is most prevalent from April to October (6). In northeastern Japan, scrub typhus is prevalent in May and June, while in southwestern Japan, it is prevalent in November and December. It is interesting to note that even in the same prefectures no simultaneous peaks in the prevalence of JSF and scrub typhus have been observed (6).

Pleocytosis and elevated protein levels were measured in the second patient's CSF during the recovery stage (Table 2). Elevated IgG antibody to *R. japonica* was measured in paired CSF specimens, indicating an association between meningitis and *R. japonica*. A few published reports describe the antibody titer to rickettsiae in CSF. Rickettsial DNAs were amplified by

TABLE 3. Clinical features and laboratory findings in four cases of JSF with meningitis[a]

Characteristic	Results for patient no.[b]			
	1	2	3	4
Fever	+	+	+	+
Skin eruptions	+	+	+	+
Tick bite eschar	+	+	+	−
Level of consciousness	Clear	Semicoma	Stuporous	Comatose
Headache	+	ND	−	+
Nausea, vomiting	+	ND	+	+
Myalgia	ND	ND	−	+
Nuchal rigidity	−	ND	+	+
Convulsions	+	+	−	Generalized
Papilledema	ND	ND	−	+
Electroencephalogram	Spike, slowing	Slowing	Normal	Delta waves
Brain CT	Normal	ND	Normal	Subdural hematoma
Pleocytosis in CSF	+	+	+	+
Protein in CSF	>45 mg/dl	>50 mg/dl	>100 mg/dl	>100 mg/dl

[a] The patient descriptions are as follows: patient 1, 59-year-old female reported by Iwamoto in 1988 (2); patient 2, 77-year-old male reported by Kodama (5) in 2001; patient 3, 58-year-old male reported in this study in 2002; patient 4, 55-year-old male reported in this study in 2002.
[b] +, positive; −, negative; ND, no description.

using nested PCR for 6 of 25 CSF specimens with scrub typhus (11). This study suggests that *R. tsutsugamushi* can cause CNS effects and that scrub typhus should be considered a causative agent of meningitis. The CSF of patients with rickettsial infection generally reveals pleocytosis with lymphocytes predominant. Therefore, JSF should be also included in the differential diagnoses of aseptic meningitis, especially in areas of JSF endemicity.

MIN, doxycycline, and new quinolones are effective treatments for JSF, while β-lactams and aminoglycosides are ineffective (12). An in vitro susceptibility study (13) demonstrated that MIN is the most potent known antibiotic for JSF. Early clinical diagnosis and prompt initiation of therapeutic doses of MIN are essential to prevent exacerbation of the disease.

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