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ORIGINAL ARTICLE

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Clinical study of Japanese spotted fever and its aggravating factors

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Abstract Twenty-eight patients with Japanese spotted fever were clinically investigated. The diagnosis was determined by confirming an increase of specific antibody. All patients were treated with minocycline, and all recovered, excluding one patient with a fulminant course. Fever and exanthema were observed in all patients, and an eschar was pointed out in 20 (71%) patients. The platelet count was $10 \times 10^4/\mu l$ or lower in 8 (28%) patients. The fibrin degradation product (FDP)-level was abnormally high, 10 μg/ml or more, in 16 (57%) patients. The creatine kinase (CK) value was high in 14 of 22 patients, suggesting the presence of myositis. The leukocyte count, FDP, C-reactive protein, and soluble interleukin 2 receptor (sIL2-R) levels were significantly higher in severe cases. In the group without concomitant steroid therapy, mean times of 54.7 h and 101.4 h were required to reduce the temperature to 38°C and 37°C or lower, respectively, after the initiation of tetracycline treatment. There were 6 severe cases: 1 with disseminated intravascular coagulation, 2 with multiorgan failure, 1 with acute respiratory distress syndrome, and 2 with meningoencephalitis. These severe cases formed a group that required 6 or more days to initiate therapy after the onset ($P < 0.005$ vs non-severe group), showing that delay in diagnosis and therapy is the major cause of aggravation. In the 2 patients complicated by multiorgan failure, the sIL2-R level, produced by activated lymphocytes, was 10000 U/ml or higher, suggesting that an sIL2-R level of more than 10000 U/ml can be used as a marker of poor prognosis. It may be better that moderate to severe cases are treated with minocycline plus short-term steroid therapy.

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Introduction

As global warming has progressed in recent years, increases in tick-borne infectious diseases have been noted, and the spread of prevalent areas has been reported.[1] Since the first case of Japanese spotted fever (JSF) was reported in Japan in 1984,[2] about 40 cases of JSF, one of the tick-borne infectious diseases, have recently been reported yearly, and the incidence is high in some regions.[3] As the case reports increase, patients with serious manifestations have occasionally been reported.[4–6] However, the aggravating factors and mortality rate of JSF have not been reviewed. In this study we clinically investigated patients with JSF to clarify the aggravating factors and clinical features.

Patients and methods

Twenty-eight patients with JSF who were admitted and treated at our hospital between April 1993 and March 2002 were clinically investigated. Excluding 1 patient who died, a definite diagnosis of JSF was determined by confirming an increase in specific IgM antibody titer in serum or a fourfold or more increase in the specific mixed (IgG, IgA, and IgM) antibody titer in paired sera, determined by the fluorescent antibody method or enzyme-labeled antibody method in the recovery stage. All patients were treated with minocycline, and the fever patterns were investigated by measuring body temperature four or more times daily after the initiation of therapy. White blood cell count, platelet count, fibrin degradation product (FDP), C-reactive protein (CRP), and creatine kinase (CK) measured on admission before therapy were investigated. In some patients, soluble interleukin 2 receptor (sIL2-R) was measured before therapy as a marker of lymphocyte activation. Aggravation

Table 1. Patients' characteristics (1)

Case no.	Age (years), sex	Onset	Eschar	Days after onset before start of therapy	Duration of fever >38°C after start of therapy (h)	Duration of fever >37°C after start of therapy (h)	Steroid therapy	Complication	Outcome
1	72 M	Jul	−	8	ND	ND	−	MOF, DIC	Dead
2	77 M	Aug	+	4	72	408	−	Meningo-encephalitis	Alive
3	49 M	Jun	+	9	12	60	+	MOF, DIC	Alive
4	66 M	Jun	+++	8	72	96	+	ARDS, DIC	Alive
5	12 M	Sep	−	5	36	72	−	DIC	Alive
6	78 M	Aug	−	6	72	336	−	Meningo-encephalitis	Alive
7	69 M	Sep	+	3	36	48	−	−	Alive
8	71 M	Sep	+	3	48	72	−	−	Alive
9	67 M	Sep	+	5	36	48	−	−	Alive
10	66 M	May	+	4	48	60	−	−	Alive
11	55 M	Aug	+	3	60	96	−	−	Alive
12	69 F	Jul	+	1	72	96	−	−	Alive
13	60 M	Aug	++	3	48	72	−	−	Alive
14	67 M	Jul	+	4	72	96	−	−	Alive
15	59 F	Jun	+	3	72	96	−	−	Alive
16	50 F	Jul	+	3	48	60	−	−	Alive
17	78 F	Aug	++	5	24	48	−	−	Alive
18	74 F	Jul	+	5	60	108	−	−	Alive
19	64 M	Jun	+	6	72	96	−	−	Alive
20	68 M	Aug	−	3	72	120	−	−	Alive
21	49 M	Aug		3	36	48	−	−	Alive
22	73 M	Aug	−	2	48	84	−	−	Alive
23	27 M	Aug	+	3	48	76	−	−	Alive
24	14 M	May	−	4	36	72	−	−	Alive
25	72 M	Aug	+	5	36	48	−	−	Alive
26	71 M	Aug		5	48	72	−	−	Alive
27	50 M	Jun	+	4	72	96	−	−	Alive
28	40 M	Nov	−	5	96	108	−	−	Alive

MOF, Multiorgan failure; DIC, disseminated intravascular coagulation; ARDS, acute respiratory distress syndrome; ND, not done

of JSF was determined by observing complications by disseminated intravascular coagulation (DIC) or organopathy such as respiratory failure and disturbance of consciousness as indices. Statistical analysis was performed using Student's *t*-test, Pearson's coefficient of correlation test, and Fisher's exact test.

Results

The patients' characteristics are summarized in Tables 1 and 2. Patients' ages ranged from 12 to 78 years, and there were 23 males and five females; that is, many patients were males. The disease onset was more frequent in summer, from May to November (Fig. 1). An eschar was pointed out in 20 (71%) patients. On physical examination, fever and exanthema were observed in all patients. The degree of exanthema varied, from generalized erythema to less noticeable cases with a few exanthemas on the trunk that may have been missed if not carefully examined. Initiation of therapy began 1 to 9 days after the onset (median, 4 days). The platelet count at initiation of therapy was $0.9 - 26.7 \times 10^4/\mu l$ and the count was $10 \times 10^4/\mu l$ or lower in 8 (28%) patients. The FDP value was abnormally high, 10 μg/ml or more, in 16 (57%) patients. The platelet count and the FDP value were negatively correlated, with $r = -0.6677$ ($P < 0.01$). The CK value was abnormally high in 14 of 22 patients in whom CK was measured on admission. There was no correlation between the CK and CRP values ($r = 0.0605$). The white blood cell count and the CRP value before therapy were positively correlated, with $r = 0.4421$ ($P < 0.05$) (Fig. 2).

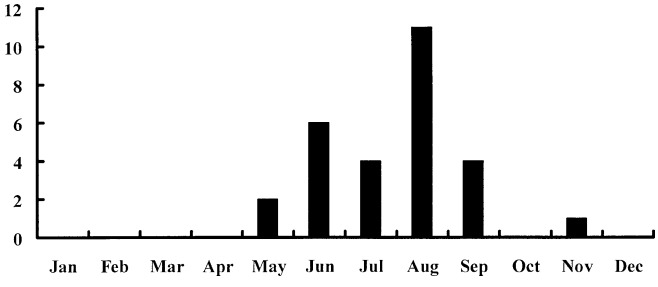

Fig. 1. Seasonal prevalence of Japanese spotted fever

The time required to reduce the fever after the initiation of minocycline treatment was investigated in 25 patients, excluding 2 who received combination therapy with steroids (because steroids influence the fever type), and 1 who died due to a fulminant course prior to the start of treatment. Mean times of 54.7 ± 17.6 h and 101.4 ± 84.8 h were required to reduce the temperature to 38°C or lower and 37°C or lower, respectively (data values are means ± standard deviation). In the analysis excluding patients complicated by meningoencephalitis, mean times of 53.2 ± 17.6 h and 77.9 ± 22.2 h were required to reduce the temperature to 38°C or lower and 37°C or lower, respectively. The number

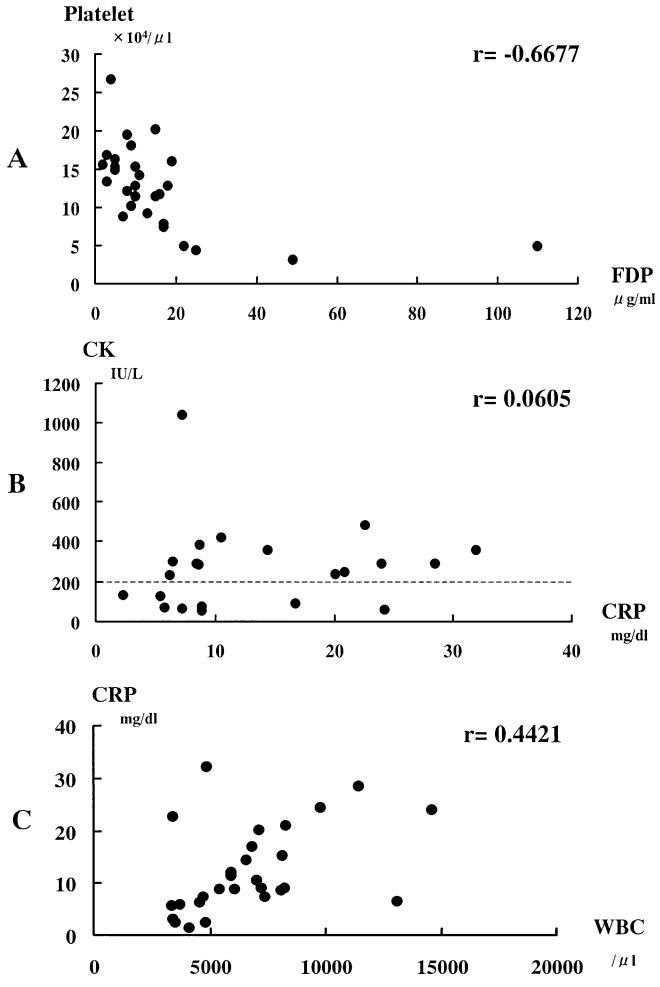

Fig. 2. **A** Correlation of platelet count and fibrin degradation product (*FDP*). **B** Correlation of creatine kinase (*CK*) and C-reactive protein (*CRP*); normal range of CK is <200 U/l. **C** Correlation of CRP and white blood cell count (*WBC*). *r*, Correlation coefficient

of days required to initiate therapy after the onset and the time required for fever reduction were not correlated ($r = 0.0155$).

There were six severe cases: disseminated intravascular coagulation (DIC) ($n = 1$); multiorgan failure (MOF) due to DIC ($n = 2$); DIC complicated by acute respiratory distress syndrome (ARDS) ($n = 1$); and complicating meningoencephalitis ($n = 2$). These severe cases formed a group that required 6 or more days to initiate therapy after the onset, and the variation in days taken to initiate therapy was significantly different between this group and the non-severe cases ($P < 0.005$) (Table 3). Excluding the one patient with the fulminant form who died within a few hours after admission to our hospital, all patients recovered. Two patients with severe cases complicated by ARDS and MOF were treated with minocycline plus steroids. The symptoms improved smoothly. In two patients complicated by MOF, the sIL2-R level was markedly high, more than 10 000 U/ml, showing excess activation of lymphocytes. Laboratory data were compared between severe cases and non-severe cases. In severe cases, the platelet count was significantly lower ($P < 0.005$), and the white blood cell count was significantly higher ($P < 0.05$). Furthermore, FDP ($P < 0.005$), CRP ($P < 0.05$), CK ($P < 0.05$), and sIL2-R ($P < 0.005$) were significantly higher in severe cases.

Discussion

Incidences of JSF were observed all year round, excluding winter, as noted in previous reports.[7] Because the only symptom is fever in patients with less noticeable erythema, the risk of misdiagnosis is high and caution is necessary. The platelet count and the FDP value were negatively correlated, and coagulation disturbance was more marked in severe cases. This finding may have reflected the pathology of rickettsiosis, that is, rickettsiae grow mainly in vascular endothelial cells and damage the endothelial cells. The high frequency of elevated CK values suggested the presence of complicating myositis. Isozyme was examined in some patients with elevated CK values, and the isozyme was MM type in all these patients (data not shown). The white blood cell count and the CRP value before therapy were positively correlated. Although leukocytosis was observed in some severe cases, it was unlikely to be caused by complication of bacterial infection, because in these patients, it took days for the diagnosis, and beta-lactam antibiotics were fully administered during that period in most patients.

In the host's protective mechanisms against infection in patients with rickettsiosis, antigen-specific T cells play a major role, and gamma interferon (γ-IFN), which is produced by activated T lymphocytes and activates macrophages, plays an important role.[8] Recent studies have reported that the levels of various cytokines, including γ-IFN, are high in the acute stage of rickettsiosis.[9,10] Severe rickettsiosis complicated by hemophagocytic syndrome has also been reported.[11] Hypercytokinemia related to the excessive activation of lymphocytes plays an important role in the pathogenesis of hemophagocytic syndrome. Leukocytosis may be related to hypercytokinemia, because the white blood cell count frequently increases in hemophagocytic syndrome.[12] The role of hypercytokinemia in severe rickettsiosis and the difference in pathogenesis among rickettsial species should be clarified.

On observation of the fever pattern, the time taken after the initiation of tetracycline treatment until the reduction of body temperature to 37°C or lower was 77.9 h, requiring 4 or more days, in patients without steroid therapy and patients without complication by meningoencephalitis. This differs from tsutsugamushi disease, in which the temperature decreases within 24 h after the initiation of treatment,[13,14] and the responses of the two diseases to tetracycline treatment were clearly different. This finding is clinically important, and suggests that caution should be taken to avoid unnecessary examinations and medication even when sufficient reduction of temperature is not obtained early after the initiation of treatment in JSF.

The majority of the patients for whom 6 or more days were required to initiate therapy after the onset had severe

Table 2. Patients' characteristics (2)

Case no.	WBC (/μl)	Platelet ($\times 10^4$/μl)	CRP (mg/dl)	FDP (μg/ml)	GOT (IU/l)	GPT (IU/l)	CK (IU/l)	sIL2-R (U/ml)
1	3400	0.9	22.6	110	394	148	478	14710
2	13130	18.0	6.5	9	133	59	296	ND
3	14600	3.1	24.0	49	168	127	288	10895
4	11450	4.3	28.5	25	130	137	289	ND
5	4720	4.8	7.3	22	43	26	1038	ND
6	8300	7.3	20.9	17	99	77	245	ND
7	7040	20.1	10.5	15	66	69	420	1251
8	5450	15.3	8.8	5	43	28	379	768
9	6820	10.1	16.8	9	104	89	89	2410
10	3370	12.1	5.5	8	40	25	123	867
11	7400	14.2	7.3	11	57	53	62	1898
12	6100	16.8	8.7	3	35	22	282	355
13	8160	15.3	15.1	10	44	33	ND	ND
14	5950	14.9	11.9	5	135	88	ND	ND
15	5950	15.5	11.3	2	80	74	ND	ND
16	4130	26.7	1.2	ND	17	8	ND	ND
17	3520	16.2	2.3	5	28	20	ND	ND
18	8240	12.8	8.9	ND	23	7	51	ND
19	5420	11.4	6.2	10	64	40	232	ND
20	6570	11.6	14.4	16	164	94	356	ND
21	4830	13.4	2.3	3	38	31	132	ND
22	8070	19.4	8.5	8	30	30	289	ND
23	3730	8.8	5.8	7	34	25	70	ND
24	3400	7.8	3.1	ND	32	17	ND	ND
25	9800	16.0	24.3	19	92	95	55	ND
26	7140	11.4	20.1	15	53	41	234	ND
27	4890	9.1	32.0	13	125	86	345	ND
28	7230	12.8	8.9	ND	243	131	73	ND

WBC, White blood cell; CRP, C-reactive protein; FDP, fibrin degradation product; CK, creatine kinase; sIL2-R, soluble interleukin 2 receptor; ND, not done

Table 3. Frequency of complicated cases

Days after onset before start of therapy	Complicated case	Noncomplicated case
≦5 Days	2	21
≧6 Days	4	1

Fisher's exact test; $P < 0.005$

disease, showing that delay in the diagnosis and therapy is the major cause of aggravation. Although the clinical diagnosis of JSF is easy in mild cases, severe cases have various complications, showing various pathological conditions, and the diagnosis is not necessarily easy, even for a physician with ample experience. A definite diagnosis of JSF is generally determined by confirming the elevation of specific antibodies during the recovery stage, but serological diagnosis is impossible in the critical stage. The polymerase chain reaction (PCR) method was recently shown to be useful with regard to specificity and rapidity in a patient who died of MOF in the critical stage of JSF.[15] The establishment of and widespread access to early diagnosis by a PCR method is expected.

For treatment, we would like to call attention to the finding that concomitant steroid therapy was effective in severe cases. Fujiwara et al.[16] reported that the prognosis was poor in patients with hemophagocytic syndrome with an sIL2-R level of more 10000 U/ml and a γ-IFN level of more than 30 U/ml. Iwasaki et al.[10] reported that the blood levels of cytokines such as tumor necrosis factor-alpha (TNF-α) and IFN-γ were high in severe cases of JSF. In our two patients with MOF, the level of sIL2-R produced by activated lymphocytes were 10000 U/ml or higher, suggesting that an sIL2-R level of more than 10000 U/ml can be used as a marker of poor prognosis. In our patients, the sIL2-R level was lower in mild cases. Because a high sIL2-R level is due to excess activation of T lymphocytes and suggests the presence of hypercytokinemia,[17] concomitant steroid therapy is appropriate for severe cases, in terms of the inhibition of abnormal activation of lymphocytes. Measurement of sIL2-R is convenient and may be useful in screening for the presence of excessive activation of lymphocytes. Because the most severe case complicated by MOF was healed by the administration of minocycline plus a single dose of 500 mg of methylprednisolone[4] and no minocycline-resistant *Rickettsia japonica* has been reported, mild cases of JSF should be treated with minocycline alone. And it may be better that moderate to severe cases are treated with minocycline plus shortterm steroid therapy. However, therapy that causes excess immunosuppression, such as steroid pulse therapy, should be carefully administered, because it has a risk of aggravating the clinical course of JSF.

Six cases (21%, including one death) were severe among the 28 patients examined in this study, and these cases may have been lethal if appropriate therapy had not been given. The mortality rate of tsutsugamushi disease was reported to be 7% in untreated classical cases, while the mortality rate of Rocky Mountain spotted fever in the pre-antibiotic era was 20%–25%, and the recent mortality rate, due to delay

in the diagnosis and therapy, was reported to be 5%.[18,19] Compared with these mortality rates, it is important to recognize that the mortality rate of JSF may be similar to that in patients with Rocky Mountain spotted fever, which is the most lethal rickettsiosis. In the future, a larger number of patients should be investigated.

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