INTERNAL✦MEDICINE

□ CASE REPORT □

A Case of Japanese Spotted Fever Complicated with Central Nervous System Involvement and Multiple Organ Failure

Ruka Nakata, Masakatsu Motomura, Masahiro Tokuda, Hideki Nakajima, Tomoko Masuda, Taku Fukuda, Akira Tsujino, Toshiro Yoshimura and Atsushi Kawakami

Abstract

Japanese spotted fever (JSF), first reported in 1984, is a rickettsial disease characterized by high fever, rash, and eschar formation. A 61-year-old man was admitted to a local hospital in Nagasaki City, Japan, after several days of high fever and generalized skin erythema. His condition deteriorated and laboratory findings indicated disseminated intravascular coagulation (DIC). The patient was transferred to our hospital with mental disturbance and status epilepticus. Treatment included minocycline, and new quinolone. Definitive diagnosis was made with a serological test showing increased antibody levels against Rickettsia japonica. Rickettsial infections are rare, but should be seriously considered for the differential diagnosis of aseptic meningitis and encephalitis, as they show no response to conventional antibiotic treatment.

Key words: Japanese spotted fever, *Rickettsia japonica*, DIC, aseptic meningitis and encephalitis

Introduction

Japanese spotted fever (JSF), caused by *Rickettsia japonica*, first reported in 1984, is a rickettsial disease characterized by high fever, rash, and eschar formation (1). Central nervous system (CNS) involvement has however been rarely reported. The prompt recognition of a rickettsial disease is often difficult, but it is important for commencing adequate antibiotic treatment. They have an excellent response to treatment which includes minocyclines and quinolones. We report a case of JSF complicated with a meningoencephalitis with neurologic symptoms.

Case: A 61-year-old man, residing in Nagayo Town, Nagasaki Prefecture, developed a high fever and shivering, with diffuse and pale erythema on his chest and extremities and he had renal dysfunction. He was admitted to a local clinic and was treated with ceftriaxone (CTRX) with no improvement in his condition, and his renal dysfunction and

inflammatory reaction worsened. Ten days after the initial symptoms, he was transferred to our hospital due to his altered mental status, seizures, and low blood pressure. On admission, his temperature was 36.7℃, blood pressure 50-60 mmHg systolic, and pulse rate 110/min. On physical examination, erythematous rash, purpura, and punctuate hemorrhages were detected on his chest and extremities, including palms and plantar surfaces. On neurologic examination, he was confused, with GCS E1V1M5. He was in septic shock leading to disseminated intravascular coagulation (DIC) and multiple organ failure (MOF).

Laboratory studies revealed leukocytosis (WBC 13,800/μL, stab 15% seg 82%), thrombocytopenia (platelet 48,000/μL), renal dysfunction (BUN 74 mg/dL, Cr 7.91 mg/dL), hepatic dysfunction (AST 164 IU/L, ALT 145 IU/L, LDH 639 IU/L), abnormal coagulation PT 74%, APTT 49.9 sec, Fib 385 mg/dl, AT-III 52%, D-dimer 36.8 μg/ml, FDP 58.0 μg/ml. ADAMTS13 activation was decreased to 29.6% (70-120%), ADAMTS inhibitor was negative and haptoglobin

was decreased to 5.1 mg/dL (19-170 mg/dL). Ferritin 2,113 U/mL, C-reactive protein 14.24 mg/dL, and sIL-2 receptor 4,669 U/mL were all elevated. Blood gas analysis demonstrated severe metabolic acidosis. Peripheral blood smear did not show increased red cell fragments. Cerebrospinal fluid analysis showed increased pressure (235 mmH$_2$O), mild mononuclear pleocytosis (10/µL), elevated protein content (186 mg/dL), and normal glucose level (114 mg/dL).

With the presentation of mental disturbance, nuchal stiffness and seizures, antibiotics were selected to cover bacterial meningitis, whereupon CTRX, vancomycin (VCM) and meropenem (MEPN) were administered intravenously. Although the typical eschar was absent, his exanthema suggested rickettsial infection, and minocycline hydrochloride (MINO) at 200 mg/day was also added intravenously. Under pharmacological sedation to control seizures, mechanical ventilation and continuous hemodiafiltration (CHDF) were administered.

Skin biopsy was performed, and the pathology revealed leukocytoclastic vasculitis and panniculitis, with the diagnosis of toxicoderma. Brain CT (Day 11) and MRI (Day 20) were normal. Bacterial meningitis was less likely with the CSF result, although mild pleocytosis and protein suggested meningoencephalitis causing mental disturbance. DIC progressed, the platelet count dropped below 10,000/µL, and his condition remained severe for a few days. With antibiotic and cardiovascular agent treatments, his condition improved. The patient became alert and his seizures were well-controlled with the use of phenytoin. Ciprofloxacin hydrochloride (CPFX) was added for the continuous low grade fever. The patient recovered both physically and mentally, and he was more energetic and talkative compared to his condition before the onset of this condition. We consulted a psychiatrist, and sodium valproate and risperidone were administered for his hypomania state. The definitive diagnosis was confirmed with paired serum testing using immunofluorescent assays, with serum antibody titers against *Rickettsia japonica* of IgM <20 and IgG <20 in the acute period (Day 8) which were increased to IgM 1:320 and IgG 1:160 in the recovery period (Day 25).

Discussion

JSF was first reported in 1984 as Rickettsiosis due to *Rickettsia japonica*; it is clinically similar to scrub typhus, but often with a more severe course (1). It is mediated by a tick carrying *Rickettsia japonica*, and more frequently seen during early summer through autumn. JSF tends to be endemic to areas along the coast of southwestern and central Japan and is associated with their warmer climate (2, 3). The first JSF in Kyusyu was reported in 1987 (4), in Nagasaki prefecture in 1999, and there have been about 1 or 2 cases annually since 2006 (5).

The symptoms of JSF include high fever, erythema, and eschar, after a 2-10 day latent period. Eschars in JSF are smaller than those seen in patients with scrub typhus, and

may disappear in a few days (3). Erythema is seen in the extremities, such as the palms and face, which may quickly spread to the trunk. Erythema on palms and soles are unique to JSF, and rarely seen in scrub typhus (6). Mahara has reported 31 patients with JSF, and their laboratory examinations are almost the same as for other rickettsioses (3). In the acute stage, leukocytosis, leukopenia, thrombocytopenia may be seen. C-reactive proteins are strongly positive, and slightly impaired liver dysfunction is commonly seen.

With a more severe disease course, cases complicated with pneumonia, meningoencephalitis, DIC, MOF have been reported (7-9). The first fatal case was reported by Kodama et al in 2002 (10). They also analyzed 21 Japanese patients with JSF to elucidate aggravating factors and showed that the severe cases formed a group requiring 6 or more days to initiate adequate therapy after onset, and had serum sIL-2 levels of more than 10,000 U/mL (11). In the present case, 11 days were required to start an adequate treatment, with moderately elevated sIL-2 receptor of 4,669 U/mL.

In the present case, severe thrombocytopenia was present, and platelet transfusion was required. Although red cell fragments were not increased in the peripheral blood smear, the thrombocytopenia, decreased haptoglobin, and decreased ADAMTS13 activity level were all suggestive of thrombotic microangiopathies (TMA). Ono et al reported that secondary ADAMTS13 deficiency could occur in patients with sepsis-induced DIC and that it had a clinical correlation with the development of renal failure (12). The endotoxemia and high cytokine levels in the circulation are thought to induce tissue factor expression and the microemboli formed in the circulation cause ischemia in a variety of organs. The present case presented severe thrombocytopenia and renal dysfunction, which may have been linked to this condition.

Diagnosis of JSF is often difficult using clinical data, and definitive diagnosis requires time. The fatal case was reported due to the delay in the initiation of adequate treatment. Conventional antibiotic therapy using β-lactamases is ineffective, and tetracyclines are the first choice (13). Although it required 11 days to initiate the appropriate treatment with tetracycline in the present case, the patient responded well and recovered from DIC and MOF. Combination therapy using new quinolone and minocycline is recommended for more severe cases (14, 15). It is advisable to consider the combination therapy, as our patient showed favorable response to new quinolone which was added for the prolonged low grade fever.

In regard to the neurological manifestations of the various rickettsial diseases, scrub typhus and Rocky Mountain spotted fever (RMSF) are frequently reported to cause CNS infection (16-18). CNS involvement in scrub typhus usually results in meningoencephalitis, confirmed on autopsy findings, and CSF pleocytosis has also been reported (17, 18). Also, CNS is the most common organ complication in RMSF, occurring in 1/5 to 1/3 of the patients (19, 20). Pathologic changes include diffuse or focal mononuclear cellular infiltration of the leptomeninges, typhus nodules (clusters

Table 1.   JSF Cases with CNS Involvement

Case	Clinical symptoms	Image·EEG	CSF	Treatment	Report
59 M	unconsciousness amnesia headache	CT:normal EEG: HVS on bil parietal, sharp wave in left central area	56/μL (47M, 9P) protein, glucose normal	MINO	Iwamoto et al, 1988 (21)
77 M	mental disturbance seizure	EEG: 3–4Hz slow wave	34/μL (24M, 10P) protein 52mg/dL glucose normal	MINO	Kodama et al, 2001 (22)
58 M	nuchal rigidity mental disturbance jaundice	CT:normal	46/μL (30M, 16P) protein 125mg/dL glucose normal	MINO	Araki et al, 2002 (23)
55 M	nuchal rigidity mental disturbance seizure DIC, MOF	CT:subdural hemorrhage EEG:diffuse slow wave	224/μL (144M, 80P) protein 116mg/dL glucose normal	MINO	Araki et al, 2002 (23)
61 M	nuchal rigidity mental disturbance seizure DIC, MOF	CT, MRI:normal EEG:normal	10/μL (M) protein 186mg/dL glucose normal	MINO CPFX	**Present case**

EEG:electroencephalogram, CNS: central nervous system, DIC:disseminated intravascular coagulation, MOF:multiple organ failure, CT:computed tomography, HVS:high voltage sharp wave, MRI:magnetic resonance imaging, M:monocyte, P:polymorphonuclear leukocyte, MINO:minocycline, CPFX:Ciprofloxacin hydrochloride.

Figure 1.   Erythema on trunk and extremity.

of microglial cells), and brain hemorrhage (17, 18). As for JSF, there have been only five reported cases with CNS manifestations including the present case (21-23). Table 1 shows the clinical features, imaging findings, and CSF findings. All patients exhibited fever and mental disturbance, including 3 patients with nuchal rigidity and 3 patients with seizures. All cases presented aseptic meningitis, with mild mononuclear pleocytosis and elevated CSF protein levels. The glucose levels are all normal. Electroencephalogram shows slow waves in 3 cases and sharp waves in 1 case. The interesting point about the present case is that the patient manifested hypomania after recovery from his serious mental disturbance. There has been no previous report re-

garding mental state alteration as a disease sequel to JSF. The patients' hypomania was not severe, and was well-controlled with medications which were gradually tapered in our psychiatry outpatient clinic.

The diagnosis was a challenge for us, since the present patient did not have an eschar, and the skin erythema may be commonly seen as a toxicodermia due to any viral or bacterial infection. The patient's history of daily gardening in the brushy home backyard in a rural area of southern Japan, a history of high fever and erythema from the early stage of the disease course, and exanthemata on the palms and soles were particularly important clues for suspecting rickettsial infection. Co-morbidity with type 2 diabetes may

have complicated his disease course causing more severe infection.

In summary, we describe a patient with JSF involving the central nervous system. Recognition of unusual manifestations and the clinical suspicion of this disease may be important for early diagnosis. It is a rare complication, but it is important to consider rickettsial infection in a patient presenting with neurologic abnormalities associated with erythema, in order to start appropriate antibiotic therapy.

The authors state that they have no Conflict of Interest (COI).

References

1. Mahara F, Koga K, Sawada S, et al. The first report of the rickettsial infections of spotted fever group in Japan: three clinical cases. Jpn J Infect Dis **59**: 1165-1172, 1985.
2. Katayama T, Furuya Y, Inada T, et al. Detection of spotted fever group Rickettsiae DNA from ticks in Kanagawa, Shimane and Kochi Prefectures. Jpn J Infect Dis **75**: 53-54, 2001.
3. Mahara F. Japanese spotted fever: report of 31 cases and review of the literature. Emerg Infec Dis **3**: 105-111, 1997.
4. Tachibana N, Shishime E, Okayama A, et al. Two cases of Spotted Fever Rickettsiosis in Kyusyu. Jpn J Infect Dis **61**: 1166-1172, 1987.
5. Nagasaki prefecture infection information center; www.pref.nagasaki.jp/kanhoken/study/.../h19/kouhannnetu.pdf.
6. Wada K, Sakaeda H, Aono R, Chiya S. Fulminant Japanese spotted fever. Jpn J Infect Dis **82**: 77-81, 2008.
7. Kodama K, Noguchi T, Chikahira Y. Japanese spotted fever complicated by acute respiratory failure. Jpn J Infect Dis **74**: 162-165, 2000.
8. Honda E, Tanioka M, Honda T, et al. 9 cases of Japanese spotted fever, including 3 cases with DIC and MOF treated at ICU. Rinsho Hihu **57**: 523-526, 2003 (in Japanese).
9. Kodama K, Senba T, Yamauchi H, Chikahira Y, Fujita H. Japanese spotted fever associated with multiorgan failure. J Infect Chemother **7**: 247-250, 2001.
10. Kodama K, Senba T, Yamauchi H. Fulminant Japanese spotted fever definitively diagnosed by the polymerase chain reaction method. J Infect Chemother **8**: 266-268, 2002.
11. Kodama K, Senba T, Yamauchi H. Clinical study of Japanese spotted fever and its aggravating factors. J Infect Chemother **9**: 83-87, 2003.
12. Ono T, Mimuro J, Madoiwa S, et al. Severe secondary deficiency of von Willebrand factor-cleaving protease (ADAMTS13) in patients with sepsis-induced disseminated intravascular coagulation: its correlation with development of renal failure. Blood **107**: 528-534, 2006.
13. Mahara F. Japanese spotted fever. Sogo Rinsho **52**: 466-470, 2003 (in Japanese).
14. Iwasaki H, Mahara F, Takada N, Fujita H, Ueda T. Fulminant Japanese spotted fever associated with hypercytokinemia. J Clin Microbiol **39**: 2341-2343, 2001.
15. Seki M, Ikari N, Yamamoto S, et al. Severe Japanese spotted fever successfully treated with fluoroquinolone. Intern Med **45**: 1323-1326, 2006.
16. Miller JR, Jubelt B. Bacterial infections. Merritt's textbook of Neurology. 8th edition. Rowland LP, Ed. Lea and Febige, Philadelphia, 1989: 125-127.
17. Silpapojakul K, Ukkachoke C, Krisanapan S, Silpapojakul K. Rickettsial meningitis and encephalitis. Arch Intern Med **151**: 1753-1757, 1992.
18. Pai H, Sohn S, Seong Y, et al. Central nervous system involvement in patients with scrub typhus. Clin Infect Dis **24**: 436-440, 1997.
19. Kirk JL, Fine DP, Sexton Dj, Muchmore HG. Rocky Mountain spotted fever: a clinical review based on 48 confirmed cases, 1943-1986. Medicine **69**: 35-45, 1990.
20. Vianna NJ, Hinman AR. Rocky Mountain spotted fever on Long Island: epidemiologic and clinical aspects. Am J Med **51**: 725-730, 1971.
21. Iwamoto K, Nishimura F, Yoshino Y, et al. A case of spotted fever with central nervous system involvement. Jpn J Infect Dis **62**: 1192-1196, 1988.
22. Kodama K, Senba T, Yamauchi H, et al. A patient with Japanese spotted fever complicated by meningoencephalitis. Jpn J Infect Dis **75**: 812-813, 2001.
23. Araki M, Takatsuka K, Kamamura J, Kanno Y. Japanese spotted fever involving the central nervous system: two case reports and a literature review. J Clin Microbiol **40**: 3874-3876, 2002.