Scholars Journal of Medical Case Reports **ISSN 2347-6559 (Online)**
Sch J Med Case Rep 2017; 5(11):801-804 **ISSN 2347-9507 (Print)**

(An International Publisher for Academic and Scientific Resources)

A Fatal Case of Japanese Spotted Fever

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Article History
Received: 22.11.2017
Accepted: 27.11.2017
Published:30.11.2017

DOI:
10.36347/sjmcr.2017.v05i11.034

Abstract: An 84-year-old female who had difficulty moving due to left hip joint pain after falling down was admitted to the Department of Orthopedics of our hospital. She had a history of operation of myoma uteri. On arrival, she had diffuse spotted erythemas in her body with a high fever (39.0 °C) and high levels of C-reactive protein (CRP) and fibrin degradation products (FDP) in addition to femur neck fracture. Orthopedicians focused on the fracture. She remained febrile and experienced thrombocytopenia progression, but she underwent internal fixation and was treated by cefazolin on the third hospital day. On the fifth hospital day in the evening, she developed labored breathing, followed by convulsion and unstable circulation. She underwent tracheal intubation and was transferred to the intensive-care unit. She was suspected of having Rickettsiae or a severe fever with thrombocytopenia syndrome. She underwent treatment with minocycline, new-quinolone, vasopressors, steroids, gamma globulin and renal replacement therapy for acute renal failure on the sixth day, but multiple organ failure with disseminated intravascular coagulation deteriorated her condition and resulted in her death on the seventh hospital day. On the same day, *Rickettsia japonica* was detected by an analysis of polymerase chain reaction from her blood and urine at a public health center. This is the fourth fatal case of Japanese spotted fever (JSF). Physicians should pay attention to increased levels of CRP or FDP on arrival in traumatized patients. Furthermore, if patients have skin lesion, thrombocytopenia or signs of inflammation, appropriate treatment for Rickettsiae diseases, including JSF, should be started immediately.
Keywords: Rickettsia japonica; Japanese spotted fever; fatal

INTRODUCTION

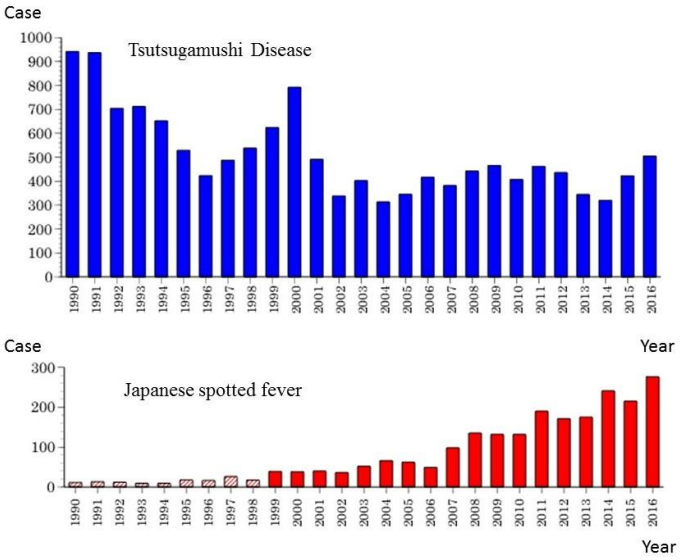
Rickettsiae are small, Gram-negative bacilli that have evolved in such close association with arthropod hosts that they are adapted to survive within the host cells, like obligate intracellular parasites [1]. Rickettsia species are transmitted by numerous types of arthropods, including chiggers, ticks, fleas and lice, and are also associated with human diseases. In Japan, diseases caused by Rickettsiae are rare, but there several types have been reported, including Japanese spotted fever (JSF), caused by *Rickettsia japonica*; Tsutsugamushi disease, caused by *Orientia tsutsugamushi*; epidemic typhus, caused by *Rickettsia prowazekii* and Q fever, caused by *Coxiella burnetii* [2]. Among them, JSF is characterized by a high fever, rash and eschar formation and is transmitted ticks. Fewer patients develop JSF than Tsutsugamushi disease, but the numbers of JSF cases are increasing annually (*Figure 1*). The incubation time is 2-8 days, and individuals over 60 years of age tend to be infected more often than younger ones. The clinical symptoms of JSF resemble those of Tsutsugamushi disease, but JSF is more severe and more often fatal (disseminated intravascular coagulation: 20%, fatalities: 0.9%)[3-5]. We herein report a rare fatal case of JSF complicating a femur neck fracture.

CASE REPORT

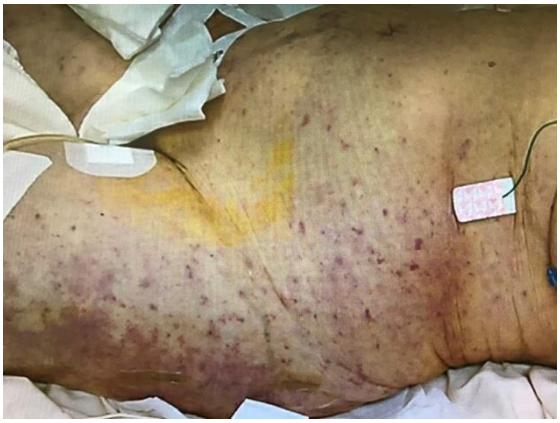
An 84-year-old female who had difficulty moving due to left hip joint pain after falling down was admitted to the Department of Orthopedics of our hospital. She had a history of operation of myoma uteri. On arrival, she had diffuse spotted erythemas in her body with a high fever (39.0 °C) in addition to left hip joint pain due to femur neck fracture. The results of the biochemical analyses of the blood on arrival are shown in Table 1. Orthopedicians focused on the femur neck fracture and did not evaluate the spotted erythemas, inflammation or thrombocytopenia. She remained febrile, and thrombocytopenia progression occurred, but she underwent internal fixation with subsequent cefazolin treatment on the third hospital day. On the fifth hospital day in the evening, she developed labored breathing, followed by convulsion and unstable circulation.

Trends in her laboratory data are shown in Table 2. She underwent tracheal intubation and was transferred to the intensive-care unit. At the time, she

was suspected of having Rickettsiae or a severe fever with thrombocytopenia syndrome based on the fact that she was still febrile and had spotted erythemas (Figure 2) and thrombocytopenia. She underwent treatment with minocycline, new-quinolone, vasopressor, steroid, gamma globulin and renal replacement therapy for acute renal failure on the sixth day, but multiple organ failure with disseminated intravascular coagulation deteriorated her condition and resulted in death on the seventh hospital days. On the same day, *Rickettsia japonica* was detected by an analysis of polymerase chain reaction from her blood and urine at a public health center.



Fig–1: The patient outbreak situation from 2007 to 2016, reported by the National Institute of Infectious Disease in Japan. Japanese spotted fever is less common than Tsutsugamushi disease, but the number of cases is increasing annually. https://www.niid.go.jp/niid/ja/tsutsugamushi-m/tsutsugamushi-iasrtpc/7324-448t.html



Fig–2: Skin lesions in the intensive-care unit. Multiple spotted and macula erythema with purpura can be seen

Table–1: Results of the biochemical analyses of the blood on arrival

white blood cells 8,300/mm^3	hemoglobin 13.8 g/dl	platelets 13.7 × 10^4/mm^3
aspartate aminotransferase 53 IU/L alanine aminotransferase 38 IU/L		
total bilirubin 1.0 mg/dl	total protein 6.3 g/dl	Glucose 129 mg/dl
blood urea nitrogen 14.1 mg/dl	creatinine 0.5 mg/dl	amylase 46 IU/L
creatine phosphokinase 236 IU/L	sodiumi 132 mEq/L	potassium 3.9 mEq/L
chloride 98 mEq/L	c-reactive protein 4.8 mg/dl.	
prothromboplastin time 13.1 (11.9) sec		
activated partial thromboplastin time 31.2 (27.4) sec		
fibrin degradation products 223.8μg/ml		

Table−2 : Time course of the laboratory data

Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
WBC (/mm^3)	8300	7000	6400	6300	15000	28900
Hb (g/dl)	13.8	12.9	11.4	12.8	10	9
Crea (mg/dl)	13.7	7.3	6.7	4.2	7.5	4.8
Crea (mg/dl)	0.75	0.66	0.71	1.6	2	2.8
ALT (IU/L)	38	62	61	72	435	1207
CK (IU/L)	236	477	1251	995	408	32874

WBC: white blood cells, Hb: hemoglobin, Plt: platelets, ALT: alanine aminotransferase, Crea: creatinine, CK: creatine phosphokinase

DISCUSSION

This is the fourth fatal case of JSF. Kodama *et al*. reported the first fatal cases among 28 patients with JSF [6]. All of the patients were treated with minocycline, and all recovered except for one fatal case with a fulminant course. The leukocyte count, fibrin degradation product (FDP), C-reactive protein (CRP) and soluble interleukin 2 receptor (sIL2-R) levels were significantly higher in the more severe cases, similar to our own. The severe cases required ≥6 or more days to initiate therapy after the onset ($P < 0.005$), showing that a delay in the diagnosis and therapy is a major cause of aggravation. Wada *et al*. reported a fatal case due to multiple organ failure with disseminated intravascular coagulation that occurred due to delayed treatment (approximately five days from the onset)[7]. Tenjin *et al*. reported on 95 cases with JSF and the first fatal case of JSF in Kumamoto Prefecture (third fatal case in Japan)[8]. They concluded that the delay (six days from the onset) in starting the proper treatment was the factor most closely related to the patient's death. However, regardless of the severity of the disease, patients treated with minocycline at an early stage (e.g. within five days after the onset) were more likely to survive their hospitalization than others treated with other agents or later after the onset. Accordingly, skin lesions, thrombocytopenia and signs of inflammation are indications of Rickettsiae diseases, including JSF, and appropriate treatment should be started immediately and continued until the confirmation of a diagnosis.

Confusion or personality changes, including poor thinking skills, difficulty focusing and sustaining or shifting attention, are behavior changes that might be caused by many problems, including infection, poor nutrition, mental health conditions or medications [9]. The patient in the present study may have had difficulty maintaining her attention due to the fever induced by JSF and fallen down by mistake, subsequently fracturing her femur neck. Increased white blood cells in the acute trauma setting are a normal result of a stress reaction; however, the CRP levels usually remain in the normal range, as it takes time for the CRP level to be increased due to interleukin-6 secretion by macrophages and T cells[10-12]. In addition, the high level of FDP was unusual in this case of femur neck fracture, a low-energy-induced trauma [13]. Accordingly, increased levels of CRP or FDP should be carefully considered with suspicion about whether or not the patient might have a significant underlying diseases that may influence the patient's outcome.

CONCLUSION

We herein reported the fourth fatal case of JSF. Physicians should pay attention to increased levels of CRP or FDP on arrival in traumatized patients. Furthermore, if patients have skin lesion, thrombocytopenia or signs of inflammation, appropriate treatment for Rickettsiae diseases, including JSF, should be started immediately.

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