【 CASE REPORT 】

# Japanese Spotted Fever with Hemophagocytic Lymphohistiocytosis

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**Abstract:**
Japanese spotted fever (JSF) is an uncommon but potentially fatal infection transmitted by tick bites. We herein report a fulminant case of JSF infection that occurred in an immunocompetent adult that was complicated by disseminated intravascular coagulation and hemophagocytic lymphohistiocytosis (HLH). We discuss the difficulty in making the diagnosis and identifying the complication of HLH in our patient. HLH is a rare complication of rickettsiosis, and this is the first reported case in English of JSF complicated by HLH in an immunocompetent adult. Secondary HLH caused by rickettsiosis requires a different treatment from primary HLH. Rickettsiosis must therefore be considered in patients with HLH.

**Key words:** Japanese spotted fever, rickettsiosis, hemophagocytic lymphohistiocytosis

## Introduction

Japanese spotted fever (JSF) is a rickettsial disease transmitted by tick bites in East Asia (1, 2). Treatment of JSF and other forms of rickettsiosis is challenging because the diagnosis is difficult. The clinical diagnosis of JSF is similar to that of other types of rickettsiosis. A fever and rash with eschar are the most typical presentation, but eschar is not always present (3). In an endemic area, the differentiation of rashes from those of true rickettsiosis and those from a reactive symptom of common viral infections or those caused by drugs is very difficult. Serologic and genetic diagnostic methods have been developed for the definite diagnosis, but these can be time-consuming to perform or may not be routinely available (4). Clinicians must therefore often begin treatment without a definite diagnosis. Accordingly, at the initial presentation, 90% cases of rickettsiosis are misdiagnosed according to one retrospective study (5).

The statistics of the National Institute of Infectious Disease in Japan indicate that approximately 1% of cases of JSF are fatal (6). While the prognosis of JSF is generally not severe, fatal cases with severe complications, such as disseminated intravascular coagulation (DIC), acute respiratory distress syndrome, and multi-organ failure, have been reported (7, 8). Avoiding these severe complications is therefore thought to be important during treatment of JSF.

Hemophagocytic lymphohistiocytosis (HLH) is a rare yet important complication of rickettsiosis (9). Primary and secondary HLH (sHLH) have been reported. Severe infection with extreme activation of cytokines is thought to be the cause of sHLH that develops in the course of rickettsiosis (10).

Cases of HLH as a complication in tsutsugamushi disease and Mediterranean spotted fever (MSF) have been reported (10, 11). JSF with HLH as a complication, however, is rare (12). We herein report the first case of JSF to be complicated by HLH in an immunocompetent adult.

## Case Report

A 71-year-old woman presented with a two-day history of a fever. Her body temperature was 38℃, and she had a rash. She had visited another clinic the day before admission to our hospital. She developed maculopapular rash in her trunk and extremities during intravenous fluid infusion (lactate Ringer's solution with 10 mg of metoclopramide) and was prescribed cefcapene, domperidone, rebamipide, esomepra-

**Table 1.** **Laboratory Data after Admission.**

| Day | 1 | 3 | 4 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|
| Blood count | | | | | | | |
| Hb [g/dL] | 11.1 | 11.2 | 11.4 | 14.1 | 12.9 | 8.1 | 10.5 |
| WBC [/μL] | 5,350 | 4,850 | 3,780 | 19,790 | 30,460 | 27,460 | 24,800 |
| SEG [%] | | | | 51 | 73 | 54 | 81 |
| STAB [%] | | | | 36 | 20 | 27 | 11 |
| Plt [×10⁴/μL] | 12 | 7.5 | 6.7 | 2.7 | 2.7 | 2.6 | 3.9 |
| Biochemistry | | | | | | | |
| Alb [g/dL] | 3.4 | 3.2 | 2.8 | 2.5 | 1.8 | 1.5 | 1.9 |
| Tbil [mg/dL] | 0.3 | 0.5 | 0.5 | 3.8 | 2.7 | 2.8 | 4.5 |
| Cre [mg/dL] | 0.84 | 0.87 | 0.98 | 3.01 | 1.62 | 1.68 | 1.70 |
| ALT [U/L] | 36 | 43 | 41 | 131 | 125 | 3,830 | 3,610 |
| AST [U/L] | 59 | 64 | 65 | 350 | 440 | 25,220 | 22,610 |
| γ-GTP [U/L] | | 63 | 60 | 147 | 82 | 71 | 115 |
| ALP [U/L] | 217 | 316 | 298 | 847 | 689 | 1,678 | 3,140 |
| LDH [U/L] | 256 | 373 | 361 | 1,082 | 1,224 | 18,660 | 19,920 |
| CRP [mg/dL] | 8.1 | | | 18.7 | 11.8 | 5.1 | 7.2 |
| Lactate [mmol/L] | | 1.7 | | 8.6 | 8.4 | 18 | |
| sIL-2R [U/mL] | | | | | 7,120 | | |
| Ferritin [ng/mL] | | | 855 | | | | |
| Coagulation | | | | | | | |
| PT [sec] | 12.8 | 12.4 | | 19.7 | 24.0 | 180 | 27.6 |
| PT-INR | 1.12 | 1.08 | | 1.75 | 2.15 | | 2.49 |
| APTT [sec] | 32.9 | 37.6 | | 62.7 | 180 | 101.7 | 118 |
| FIB [mg/dL] | | | | 172 | 112 | 30 | 57 |
| FDP [μg/mL] | | | | 149.9 | 28.3 | 13.1 | 12.7 |
| AT3 [mg/dL] | | | | 34.1 | 34.9 | 39.3 | |

Hb: hemoglobin, WBC: white blood cell, SEG: segmented form neutrophil, STAB: band form neutrophil, Plt: platelet count, Alb: albumin, Tbil: total bilirubin, Cre: creatinine, ALT: alanine aminotransferase, AST: aspartate aminotransferase, γ-GTP: gamma-glutamyl transpeptidase, ALP: alkaline phosphatase, LDH: lactate dehydrogenase, CRP: C-reactive protein, sIL-2R: soluble interleukin-2 receptor, PT: prothrombin time, INR: international normalized ratio, APTT: activated partial thromboplastin time, FIB: fibrinogen, FDP: fibrin/fibrinogen degradation products, AT3: antithrombin III

zole, bifidobacterium, acetaminophen, and loxoprofen. No pustular formation was found, and the patient's palms and soles were intact.

Her vital signs were body temperature 36.5℃, blood pressure 116/56 mmHg, pulse rate 79/min and respiratory rate 12/min. She had visited the Rokko Mountains, a known endemic area of JSF and tsutsugamushi disease, several times within the previous two weeks. Her general appearance was unremarkable, and no eschar was found. Drug-associated rash and viral infection were suspected, so only acetaminophen was continued for symptomatic relief. Later on the same day, she visited the emergency department again and requested a blood test (Table 1). Her vital signs were body temperature 38.8℃, blood pressure 122/58 mmHg, pulse rate 86/min, and respiratory rate 27/min. Only mild elevation of the values of aspartate aminotransferase (AST: 59 U/L) and C-reactive protein (CRP: 8.1 mg/dL) were found, and a follow-up visit was scheduled three days later.

The next day, the patient visited another hospital, as she had begun vomiting. Non-contrast chest and abdominal computed tomography was conducted to investigate the cause of the fever and vomiting, but there were no specific findings. She returned to our hospital due to severe appetite loss on day 3, one day before the scheduled appointment. She was able to eat small fruits and soft meals and could drink 500 to 1,000 mL of water every day. Her vital signs were a body temperature of 39℃, blood pressure 107/54 mmHg, pulse rate 70/min, and respiratory rate 20/min. Her rash was milder than two days before, and no petechiae or exanthema were found.

Laboratory data showed hyponatremia, thrombocytopenia, and elevated values of AST (Table 1). She was hospitalized for a further evaluation. On day 4, her fever persisted, and her thrombocytopenia had worsened, with a platelet count of 6.7×10⁴/μL with pseudo Pelger-Huët anomaly. To evaluate the possibility of myeloid leukemia, a bone marrow biopsy was performed, but there were no apparent blasts. On days 5 and 6, she remained febrile, but other vital signs were unchanged. On day 7, whole-body petechiae appeared, and thrombocytopenia progressed (Fig. 1, Table 1). Laboratory data showed a serum creatinine level of 3.01 mg/dL, total bilirubin 3.8 mg/dL, alanine aminotransferase (ALT) 131 U/ L, platelet count 2.7×10⁴/μL, prothrombin time 19.7 seconds, activated partial thromboplastin time 62.7 seconds, fi-
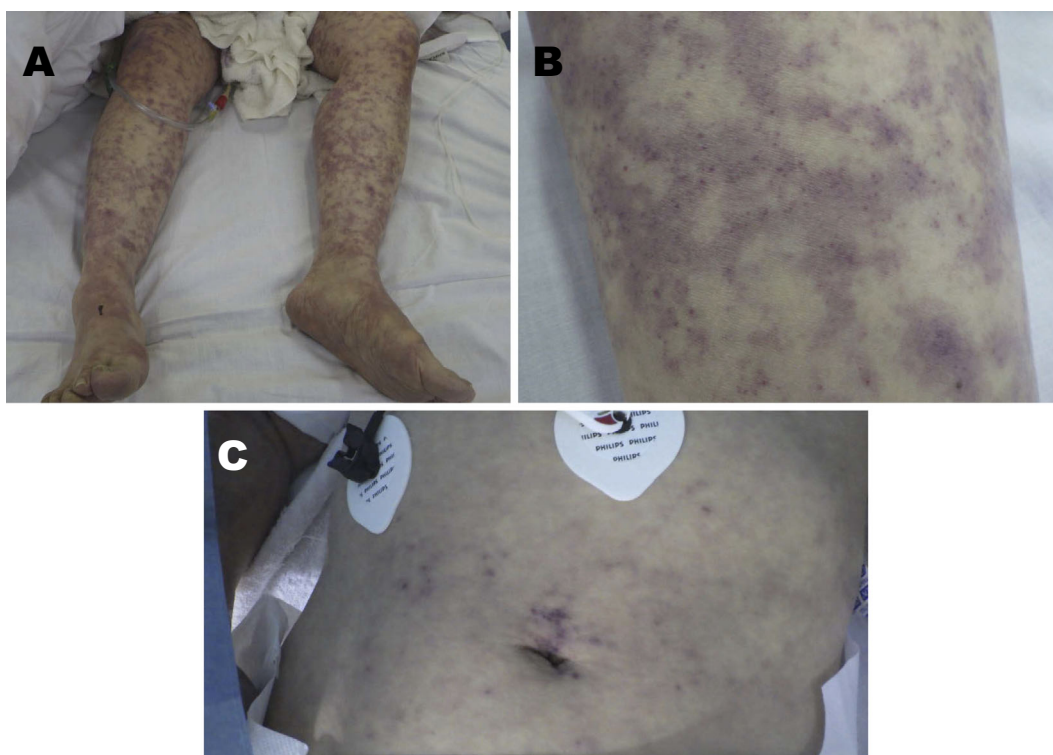
**Figure 1.   General petechiae and purpura. On day 7, petechiae and purpura developed on the whole-body surface. A and B show the feet, while C shows the trunk.**

**Table 2.   Clinical Characteristics, Therapy and Prognosis of 27 Cases of Rickettsiosis with HLH.**

| reference | age [years] | rickettsia | S to T [days] | treatment | prognosis |
|---|---|---|---|---|---|
| (12) | 0 | *Rj* | unknown | MINO, IVIG | L |
| (9) | 11 | *Cb* | unknown | unknown | L |
| (9) | 3, 38 | *Rc* | unknown | unknown | 2L |
| (10) | 5 | *Rc* | 5 | CPL, CLM | L |
| (27) | 5 | *Ot* | 8 | DOXY | L |
| (28) | 58 | *Ot* | 24 | DOXY | L |
| (28) | 37 | *Rc* | 19 | DOXY | L |
| (30) | 0 | *Ot* | 18 | DOXY, Blood, DEX | D |
| (32) | 16, 24, 33 | *Ot* | unknown | CPL | 3L |
| (33) | 0 | *Ot* | 10 | IVIG, DOXY | L |
| (35) | 7, 7, 9 | *Ot* | unknown | DOXY, AZM | 2L1D |
| (36) | 34 | *Ot* | 8 | MINO, DEX | D |
| (37) | 0 | *Ot* | 8 | CLM, DEX, ETP | L |
| (38) | 9 | *Ot* | unknown | ROX, ETP, CyA, DEX, MTX, CPL | L |
| (39) | 22 | *Ot* | 13 | DOXY | L |
| (42) | 0 to 11 | *Ot* | unknown | DOXY, AZM, IVIG, Blood+/- mPSL | 5L1D |
| (11) | 53 | *Ot* | unknown | MINO | L |

HLH: hemophagocytic lymphohistiocytosis, S to T: days from symptom onset to appropriate treatment initiation, Rc: Rickettsia conorii, Rj: Rickettsia japonica, Cb: Coxiella burnetii, Ot: Orientia tsutsugamushi, MINO: minocycline, IVIG: intravenous immunoglobulin, CPL: chloramphenicol, PSL: prednisolone, blood: blood product, DOXY: doxycycline, AZM: azithromycin, DEX: dexamethasone, ETP: etoposide, FOY: gabexate mesylate, ROX: roxithromycin, CLM: clarithromycin, CyA: cyclosporine, MTX: methotrexate, mPSL: methylprednisolone, D: death, L: alive

brinogen 171 mg/dL, and fibrin/fibrinogen degradation products 149.9 μg/mL. Acute kidney and liver failure and DIC were diagnosed.

Her blood pressure decreased to 80/50 mmHg with atrial fibrillation. It was early September, which is a highly en-demic season of JSF in our area, so severe JSF was suspected. Minocycline and levofloxacin were started in accordance with a previous report of severe JSF (13). Bolus acetated Ringer's solution infusion was also started immediately for sepsis. Samples were sent to the Mahara Institute of
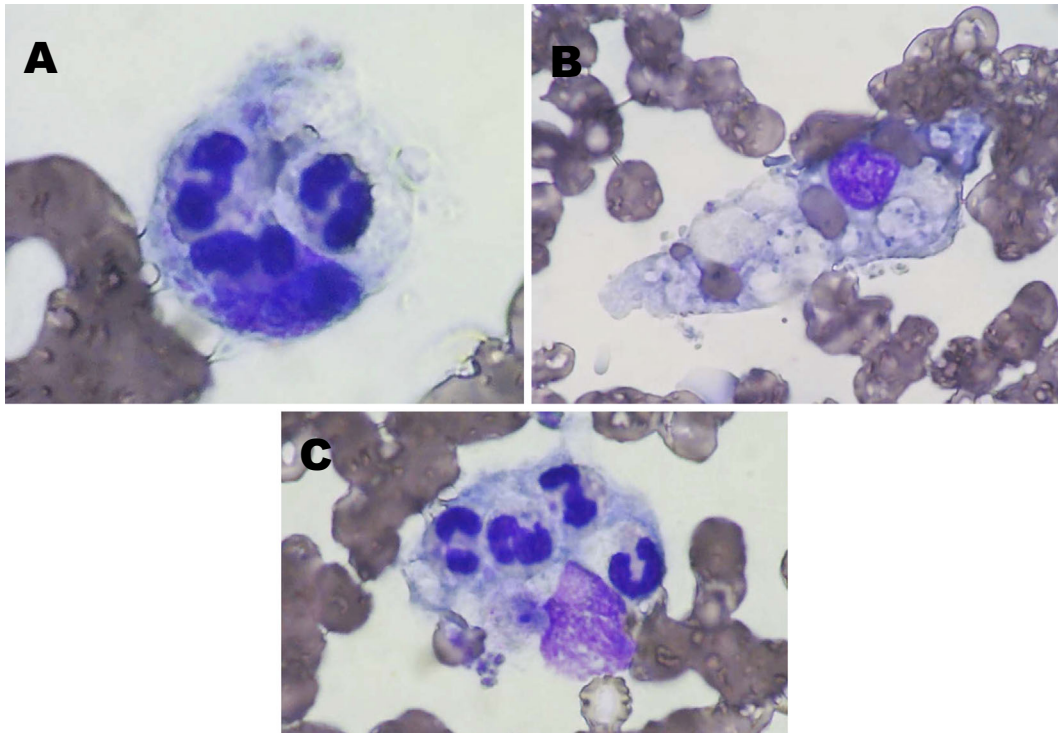
**Figure 2.   Bone marrow aspiration smear of hemophagocytosis. A: Platelets and polynuclear neutrophils are phagocytosed by macrophages. B: Erythrocytes are phagocytosed by macrophages. C: Polynuclear neutrophils are phagocytosed by macrophages [May-Grünwald-Giemsa (MGG) stain; original magnification 1,000].**

Medical Acarology and Hyogo Prefectural Institute of Public Health Science for a serological analysis and polymerase chain reaction (PCR) analysis for *Orientia tsutsugamushi* (*Ot*), *Rickettsia japonica* (*Rj*), and severe fever with thrombocytopenia syndrome virus (SFTSV).

Her respiratory status deteriorated during the first six hours after treatment started, and she was transferred to the intensive-care unit (ICU). Intubation was performed for progressive respiratory failure and shock. Noradrenalin up to 0.4/μg/kg/min was started for hypotension, followed by vasopressin (0.03 U/min) and glucocorticoid (hydrocortisone 200 mg/day) for septic shock unresponsive to catecholamine. Continuous hemodiafiltration was also started for anuria, and blood and platelet transfusion and anti-DIC agents (human anti-thrombin III agent and recombinant human soluble thrombomodulin alpha) were added for acutely progressive anemia, thrombocytopenia, and DIC. Despite the appropriate dosage of antibiotics and the maintenance of hydration, blood transfusion, ventilation, and hemodiafiltration, the patient's condition progressively deteriorated. She ultimately died five days (day 11) after admission to the ICU.

The results of outsourced samples were returned just before and after her death. Bone marrow aspirate showed hypocellularity and hemophagocytes (Fig. 2), and all other data (fever >38.5℃, minimum platelet count $2.6×10^4/μL$, minimum hemoglobin concentration 8.1 g/dL, serum ferritin 855 ng/mL, and soluble interleukin (IL)-2 receptor 7,120 U/ mL) were consistent with the diagnostic criteria of

HLH (14). The PCR analysis for *Rj* was positive, and serologic testing for *Rj*, SFTSV, and *Ot* strains were all negative using the immunoperoxidase method, while only *Rj* was positive on an immunofluorescence assay (IgG and IgM titers on the day of ICU admission =1:80 and 1:80; IgG and IgM titers on the third day of care in the ICU =1:160 and 1: 320, respectively). The final diagnosis was JSF complicated by DIC and HLH.

## Discussion

Our fatal case of JSF was difficult to diagnose at the initial presentation and was complicated by HLH. JSF is an uncommon disease but largely treatable with simple antibiotic therapy. It is a 'must-not-miss' differential diagnosis for clinicians working in an endemic area (2). Serologic or genomic diagnoses are often not rapidly available, and the definite diagnosis is commonly made four to five days after blood samples are collected. Theoretically, treatment should therefore be started when rickettsiosis is first suspected (15). According to a Japanese cohort study of *Ot* and *Rj* infection, being in an endemic area and the presence of a fever, rash, and eschar are the most common signs among patients with tsutsugamushi disease or JSF (3). Although eschar is thought to be the most specific sign for rickettsiosis, clinicians should be aware that about 10% of patients have no eschar (3). In our case, the lack of evidence of any tick bites delayed the initiation of treatment. To our knowledge, no

studies have examined the factors underlying treatment delay of JSF or other rickettsiosis entities. The lack of eschar, however, has been proposed as an important factor influencing the delay in the initial diagnosis of rickettsiosis in some studies and has also been reported to be related to a poor prognosis (16-18). Our patient did not have severe physical or laboratory abnormalities at presentation, but the absence of eschar alone indicated a poor prognosis. Physicians should carefully follow patients, even without signs of eschar, and continue to search for such signs when rickettsiosis is suspected.

In the presently reported case, we began JSF-specific treatment seven days after the patient's first admission (eight days after the onset of symptoms). Treatment delay is thought to be one of the worst prognostic factors for rickettsiosis in general, and we believe that it contributed to the fatality in the present case (15). Several cohort studies that investigated prognostic factors of rickettsiosis, however, showed inconsistent data. For example, one cohort of patients with JSF showed a significant correlation between treatment delay and the disease severity (7), but another claimed that there was no such correlation (19). Two cohort studies targeting tsutsugamushi disease also showed no significant relationship between the severity and days from the symptom onset to the initiation of appropriate antibiotics (16, 18), while another study concluded that the number of days from hospital admission to the initiation of treatment affected the disease prognosis (20). In a cohort of Rocky Mountain spotted fever (RMSF), the number of days from the symptom onset to doxycycline initiation was a significant factor influencing a fatal prognosis (21). Of note, these studies varied in sample size (n= 28 to 297), in their definitions of treatment delay (days from symptom onset to treatment or days from admission to treatment), and in outcomes (severity, development of complication, or death). Therefore, whether or not treatment delay is truly related to the prognosis of rickettsiosis remains controversial, and a further study is needed. In or near an endemic area, if patients present with a rash and fever without eschar, clinicians should consider beginning empiric therapy.

We initially treated this case as one of septic shock with DIC but eventually discovered it was complicated by HLH. HLH is classified as either primary or secondary according to the underlying etiology. Although we did not perform genetic testing for this patient, we made a clinical diagnosis of sHLH based on the patient's older age and obvious infectious trigger. The diagnosis of sHLH is still being debated, however, because the diagnostic criteria of HLH were compiled for primary pediatric HLH (22). Several modified criteria have been proposed, but this case met the HLH-2004 criteria, the most accepted criteria (14, 23). Rickettsiosis was complicated by HLH in several reported cases, but in a patient with JSF, complication by HLH is rare. To our knowledge, only one case in a three-month-old infant has been reported in English (12). sHLH is not age-dependent but mainly occurs in older children and adults depending on the

immunological background. The currently reported case is the first case of JSF complicated by HLH in an immunocompetent adult.

There is no standard therapy for sHLH because of the heterogenicity of the underlying diseases (14, 22, 23). HLH with rickettsiosis is a rare presentation, but several cases have been reported. A *PubMed* search of HLH cases with rickettsiosis showed 25 reports of rickettsiosis with sHLH (9-12, 24-44). Twenty-seven cases were extracted from 15 of the reports (Table 2), and the other 10 (24-26, 29, 31, 34, 40, 41, 43, 44) and several cases (9) were not used due to not matching the diagnostic criteria of HLH or a lack of detailed English information. The pathogens were mainly *Ot*, but other types of rickettsia were also reported (21 *Ot*, 4 *R. conorii*, 1 *Rj*, 1 *Coxiella burnetii*). The treatment strategies were mainly antibiotics. Twelve cases were treated with rickettsia-specific antibiotic therapy only (e.g. doxycycline, clarithromycin, or chloramphenicol), two cases were administered antibiotics with intravenous immunoglobulin (IVIG), eight were given antibiotics with systemic steroids with or without IVIG, two were given antibiotics with systemic steroid therapy and chemotherapy (etoposide, and/or cyclosporine), and the treatment was unknown in three cases. Twenty-three cases survived, and four died.

In our case, we used double antibiotics specific to *Rj* with systemic steroids. Chemotherapy was an option, but because the vital status of our patient was severely unstable, cytotoxic agents were withheld. Although our patient ultimately died, complication with sHLH *per se* is not an untreatable sign of rickettsiosis (25/29 survived). Most cases are cured by rickettsia-specific treatment only, and the clinical importance of sHLH in treatment of rickettsiosis is still unknown. In the present case, bicytopenia was controlled by blood transfusion, and we believe that the fatal course was mainly caused by sepsis and DIC induced by JSF. When clinicians detect HLH, it is important that they consider rickettsiosis and plan the treatment accordingly. There is no standard treatment for infection-induced sHLH, and only specific antimicrobial treatment is strongly recommended by the current expert consensus (23). Clinicians should therefore be aware that rickettsiosis is a 'must-not-miss' cause of sHLH.

## Conclusion

JSF is a rare but possible cause of sHLH. Clinicians should consider the possibility of rickettsiosis in patients with exposure to an endemic area and who have rashes but not eschar. Rickettsia-specific antibiotics are important for the treatment of rickettsiosis with sHLH.

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

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