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Prompt Diagnosis and Treatment of Japanese Spotted Fever with an Atypical Triad of Clinical Symptoms: A Case Report

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Abstract: Japanese spotted fever (JSF) is a neglected and potentially fatal infectious disease. Delays in diagnosis and treatment of JSF are important causes of poor prognosis. We report a case of JSF in a 75-year-old farmer who, following autumn field work in Sichuan, China, presented with an atypical triad of clinical symptoms: high fever, petechial rash, and notably no eschar. Without appropriate diagnosis and treatment, she developed septic shock and acute respiratory distress syndrome. The diagnosis of JSF was confirmed by the identification of *Rickettsia japonica* by metagenomic next-generation sequencing (mNGS) of the blood. After one week of treatment with doxycycline, the patient's clinical symptoms subsided without any complaints of discomfort.

Keywords: atypical triad of clinical symptoms of Japanese spotted fever, *Rickettsia japonica*, mNGS

Introduction

Japanese spotted fever (JSF) is a rickettsiosis of the spotted fever group caused by *Rickettsia japonica*, which is transmitted by the bite of arthropods (mainly ticks) and was first diagnosed in Japan in 1984.[1] In recent years, the incidence of tick-borne rickettsioses in China has gradually increased,[2,3] and JSF has shown a tendency to disseminate and its geographic distribution has continued to expand, suggesting that the prevalence of *Rickettsia japonica* in China may be more widespread than previously thought.

JSF is often thought to cause mild symptoms, and with limited knowledge of the epidemiology of JSF and insufficient recognition of potential cases, the incidence and potential lethality may be grossly underestimated, posing a serious risk to human health. High fever, petechial rash, and eschar are the triad of clinical symptoms of JFS,[4] and thrombocytopenia, elevated CRP, and eosinophilia are found in most patients. A retrospective study conducted by the National Institute of Infectious Diseases in Japan showed that,[5] compared to high fever (99%) and rash (94%), eschar (67%) are not universally present, and subsequent studies have been consistent with this finding.[6–8] The lack of evidence of eschar and the limitations of molecular diagnostic techniques in the laboratory usually lead to delays in the diagnosis and treatment of JSF and the development of multiple complications, such as disseminated intravascular coagulation, syndrome, phagocytosis lymphohistiocytosis, and multiorgan failure, which can cause death.[9]

This article reports a critical case of Japanese spotted fever in an elderly woman in Sichuan, China, who was misdiagnosed with "pulmonary infection and drug allergy" due to a lack of evidence of eschar and who was promptly diagnosed pathogenetically by metagenomic next-generation sequencing (mNGS), letting her be appropriately treated with doxycycline antibiotics, after which she had no complaints of discomfort.

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Case Report

A 75-year-old female, Guangyuan, Sichuan Province, with no history of chronic disease, developed fever on August 25, 2023 after working in the field (max temperature 40.5°C), which was restored to normal for a short period of time by antipyretic drugs. Fever was accompanied by dizziness, fatigue, swelling and pain in the forehead, nausea, and vomiting, and it was aggravated by petechial rash and respiratory distress after 2 days. The primary hospital diagnosed the patient with "lung infection and drug allergy". Blood culture, respiratory throat swabs, and bronchoalveolar lavage fluid from bronchoscopy were negative. She was given (successively, empirically) penicillin, ceftriaxone, meropenem and other anti-infective agents; methylprednisone, which is an anti-inflammatory agent; and other treatments. However, she did not improve and went into shock. The petechial rash spread from her abdomen to her limbs and palms, with more on the abdomen and less on the limbs and palms. The rash was not raised above the skin surface, did not discolor when pressed, did not itch, and was not painful or bleeding. The skin was normal between the petechial rash spots. She denied a history of close contact with pets or poultry of insect bites.

On August 31, she was transferred to the Department of Infectious Diseases of the General Hospital for acute respiratory distress syndrome. Physical examination: body temperature 39.4°C, heart rate 124/min, respiration 26/min, blood pressure 82/50 mmHg, PaO_2 86%, sequential organ failure assessment (SOFA) score 6. Drowsiness, acute illness, turbidity on percussion in both lower lungs, coarse breath sounds in both lungs, and distinct wet rales were heard. A petechial rash was visible on the abdomen and extremities that did not fade with pressure (Figure 1). She had mild generalized depressed edema, but no eschar.

Laboratory analysis revealed a marked increase in C-reactive protein (CRP) (161.35 mg/L), procalcitonin (0.66 ng/mL), alanine transaminase (114.2 IU/L) and aspartate transaminase (175.6 IU/L); a marked decrease in eosinophils (0.00 $x10^9$/L) and PLT (62 $x10^9$/L); and abnormal WBC (4.90 $x10^9$/L), NE (4.27 $x10^9$/L), L (0.466 $x10^9$/L), IL6 (154.03 pg/mL), IL10 (18.29 pg/mL), ALB (31.2 g/L), and BNP (270.35 pg/mL). A computed tomography (CT) scan of the chest revealed localized thickening and adhesion of the right pleura and a small amount of bilateral pleural effusion (Figure 2). The rest of the laboratory tests were negative, and image examination showed no abnormalities. Atypical pathogenic bacterial infection was suspected. Because of the lack of eschar, her blood was tested by mNGS, and the results of the mNGS on September 2 showed that *Rickettsia japonicum* (genus Rickettsia relative abundance 82.7%, sequence 36. species Rickettsia japonicum, confidence level 99%, sequence 3). No other disease-causing viruses or bacteria were found in the report. The patient was diagnosed with Japanese spotted fever and treated with doxycycline (first dose 0.2 g, 0.1 g bid po sequential treatment) and antishock treatments. The patient's general condition was good on September 7 (Figure 3 and Table 1). During the follow-up period, the patient did not complain of discomfort, and laboratory tests did not reveal any abnormalities.

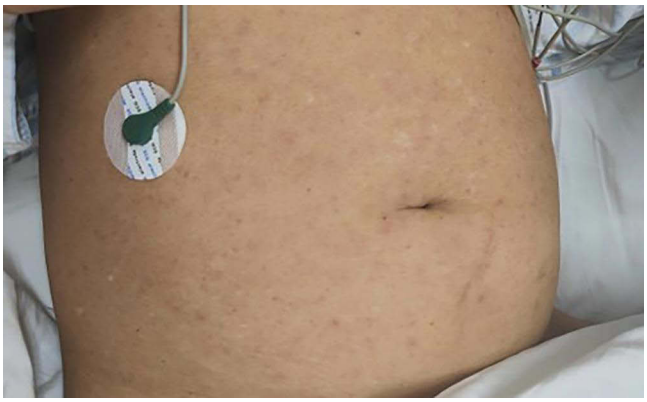

Figure 1 Petechial rash on the abdomen.

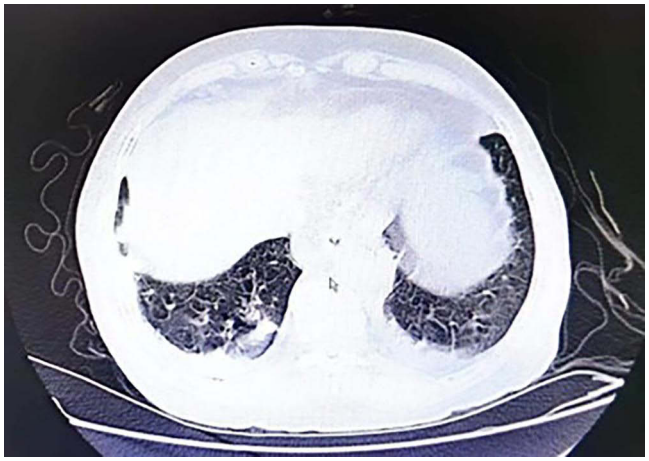

Figure 2 CT revealed localized thickening and adhesion of the right pleura and a small amount of bilateral pleural effusion.

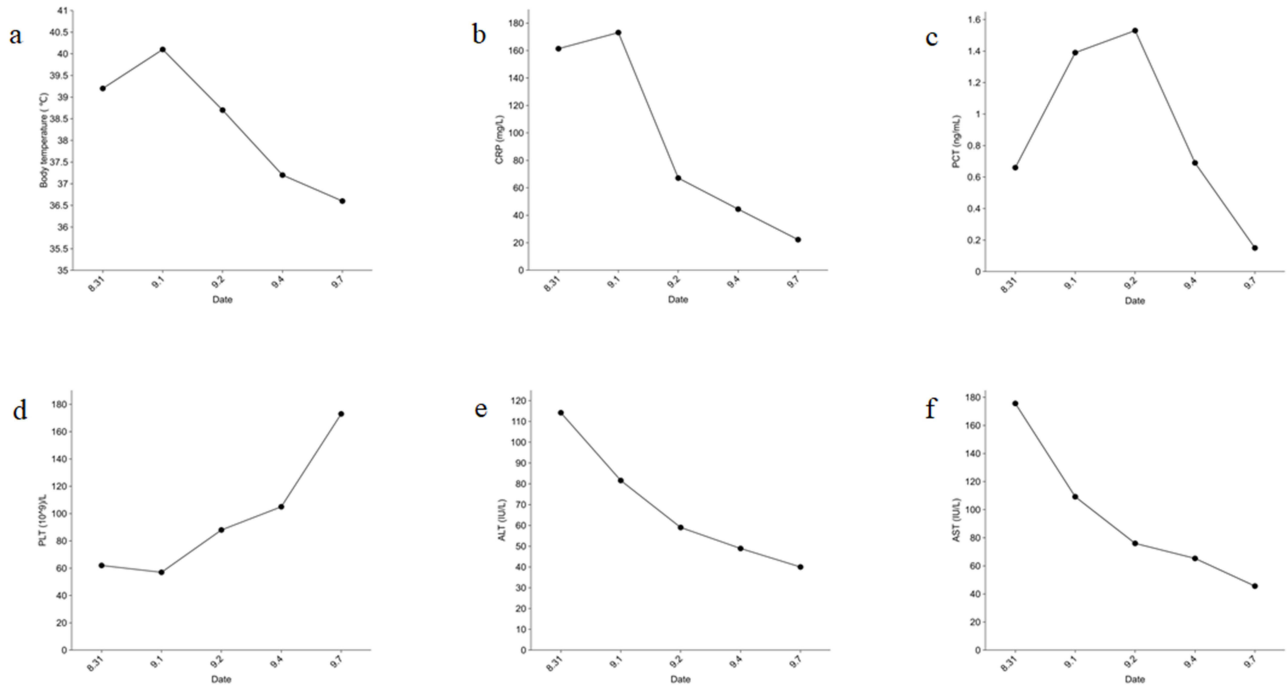

Figure 3 Body temperature and laboratory indices during hospital stays. (**a**) The tendency of body temperature (°C) during hospital stays. (**b**) The tendency of high-sensitivity C-reactive protein value (mg/L) during hospital stays. (**c**) The tendency of procalcitonin value (ng/mL) during hospital stays. (**d**) The tendency of platelet value (10^9/L) during hospital stays. (**e**) The tendency of alanine aminotransferase value (U/L) during hospital stays. (**f**) The tendency of aspartate aminotransferase value (U/L) during hospital stays.

Discussion

JSF is a zoonotic infectious disease with *Rickettsia japonica* as the source of infection and the bite of arthropods (ticks, lice and mites) as the route of transmission, with ticks being the main source of transmission. It was found that *Rickettsia japonica* infection was detected in eight species of three genera of ticks (*Haemaphysalis, Dermacentor* and *Ixodes*), and that *H. flava* and *H. longicornis* were the important vector ticks of JSF. In China, the main vector of JSF is probably the *Haemaphysalis longicornis*, which is widely distributed in eastern China.[2] The onset of the disease is distinctly seasonal, occurring more frequently from early summer to fall in patients with a history of outdoor activities in jungles, wilderness, and farmland. The triad of high fever, petechial rash, and eschar is a typical clinical presentation of JSF, accompanied by progressive thrombocytopenia, elevated CRP, and elevated liver enzymes during the course of

Table 1 Body Temperature and Laboratory Indices During Hospital Stays

Date	Temperature Max, °C (36.0–37.0)	C-Reactive Protein, mg/L (0.0–3.0)	Procalcitonin, ng/mL (<0.05)	Platelet, 10^9/L (125.0–350.0)	Alanine Aminotransferase, IU/L (9.0–60.0)	Aspartate Aminotransferase, IU/L (15.0–45.0)
Aug. 31	39.2	161.35	0.66	62	114.2	175.6
Sept. 1	40.1	173.11	1.39	57	81.6	109.2
Sept. 2	38.7	67.11	1.53	88	59	76
Sept. 3	37.2	44.46	0.69	105	48.9	65.3
Sept. 7	36.6	22.24	0.15	173	40	45.6

the disease. Since the first case of JSF in China in 2013, scattered cases have been reported in Zhejiang, Sichuan, Hunan and Hubei provinces,[7,10,11] reflecting the widespread nature of the disease in China. The unclear history of arthropod exposure, incomplete presence of the typical triad and limitations of molecular diagnostic techniques in the laboratory have led to a relatively high rate of misdiagnosis, serious complications and risk of death. The absence of eschar was the main reason JSF was not suspected in the primary hospital in this case. Studies have shown that 60% of patients with JFS present with eschar, but 90.0% of patients with JFS present with fever, petechial rash, elevated CRP and eosinopenia, suggesting that fever, petechial rash, elevated CRP and eosinopenia are good markers of JSF when there is no evidence of eschar,[8] which is supported by clinical evidence in this case. The commonly used techniques of immunofluorescence, enzyme-linked immunosorbent assay and quantitative polymerase chain reaction for pathogenetic diagnosis are slightly less timely and less often positive for diagnosis, especially in patients without evidence of eschar. Rapid and accurate diagnosis via mNGS is invaluable for providing early etiologic therapy, reducing complications, and decreasing morbidity and mortality.[12,13] In nonspecific cases of JSF, mNGS can provide ideas for pathogenetic diagnostic diagnosis. Blood mNGS in this case facilitated the initiation of precision therapy and avoided serious complications to some extent.

Rickettsia japonica is a specialized intracellular gram-negative bacterium, and the judicious use of antibiotics is critical to the prognosis of JSF.[2] Its treatment has not yet been standardized.[14] Tetracyclines, especially doxycycline and minocycline, are the first-line drugs for the treatment of JSF. When JSF is suspected, empirical treatment with tetracyclines can be used to avoid rapid disease progression when contraindications are ruled out.[15] Some case reports have shown that the combination of omadacycline and omadacycline combined with moxifloxacin is advantageous in the treatment of severe rickettsial infections, fluoroquinolones in combination with tetracyclines have an advantageous regimen in reducing fever during the patient's clinical course,[9,14,16] and it is agreed that β-lactams and aminoglycosides cannot enter the cellular compartments and are ineffective against JSF. This is the main reason for the ineffectiveness of empirical anti-infective treatment of the present patient in the primary hospital, which should be emphasized by clinical practitioners.

Conclusion

In geographic areas with tick-borne vectors, patients presenting with unexplained high fever and petechial rash should be considered for Japanese rickettsial infections. Early initiation of tetracycline-based anti-infective therapy, along with appropriate testing, is crucial for timely diagnosis and treatment of JSF, thereby reducing the rates of critical illness and fatalities.

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Consent for Publication

Written informed consent was provided by the patient for the publication of the case details and images. Details of the case can be published without institutional approval.

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Disclosure

The authors report no conflicts of interest in this work.

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