Scrub typhus (Tsutsugamushi disease) in a patient presenting with hemophagocytic syndrome

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ABSTRACT
Scrub typhus is a mite-borne infectious disease caused by Orientia tsutsugamushi, which is found mainly in East and Southeast Asia and in Australia. The disease presents with a variety of non-specific symptoms, including fever, headache, cough, myalgia, and rash. Delay in starting appropriate antimicrobial therapy may lead to serious complications and even death. We report the case of an 84-year-old Japanese patient with scrub typhus who developed hemophagocytic syndrome (HPS) and was successfully treated with minocycline in addition to corticosteroids. A pathognomonic skin ulcer on her right buttock, which was initially covered with black eschar, prompted us to consider the possibility of scrub typhus. Blood polymerase chain reaction and antibody assays confirmed the diagnosis. Scrub typhus must be considered as one of the underlying diseases that may cause HPS in patients living in the Asia-Pacific region and in those who have recently returned from endemic areas.

1. Introduction
Hemophagocytic syndrome (HPS), also known as hemophagocytic lymphohistiocytosis, is an immune-mediated life-threatening syndrome characterized by excessive immune activation. The syndrome occurs as a consequence of a genetic defect in natural killer cells or cytotoxic T-cells, infection, autoimmune disease, or malignancy. HPS is usually progressive, and delays in diagnosis and starting appropriate treatment may be fatal. Treatment of HPS depends on the cause. In patients who have HPS in association with infection or malignancy, treatment of the underlying condition is crucial for controlling the hyperimmune activation in this syndrome. Therefore, physicians who treat patients suspected of having HPS need to identify the trigger for this syndrome. Here, we describe the case of a Japanese woman with HPS in association with scrub typhus, a mite-borne infectious disease caused by Orientia tsutsugamushi, which is endemic in the Asia-Pacific region.

2. Case report
An 84-year-old rural-dwelling Japanese woman presented to our clinic in April 2016 with a three-day history of high-grade fever and skin rash. She also complained of malaise, loss of appetite, and dyspnea. Central nervous system symptoms such as headache and confusion were not observed. Physical examination revealed body temperature of 40.2°C, blood pressure of 112/80 mmHg, and pulse rate of 128 beats/min. Oxygen saturation was 90% on room air. Coarse crackles were audible in both lower lung fields. Heart sounds were clear. Skin examination revealed pale erythematous 5–10-mm lesions scattered over the trunk and a skin ulcer on her right buttock (Figure 1) that was covered with black eschar. There was no significant lymphadenopathy on physical examination.

Laboratory investigations revealed leukocyte count of 7040/μL (neutrophils 6899/μL), hemoglobin level of 11.6 g/dL, and platelet count of 4.3 × 10^4/μL. Serum C-reactive protein was markedly elevated at 21.7 mg/dL. Serum creatinine and blood urea nitrogen were normal at 0.45 and 16 mg/dL, respectively. Liver function tests were normal. Serum lactate dehydrogenase (LDH) and ferritin were elevated at 447 IU/L and 2128 ng/mL, respectively. Serum soluble interleukin-2 receptor level was elevated at 3950 U/mL. Plasma fibrinogen was normal at 312 mg/dL (normal 160–380) and fibrinogen degradation products were slightly elevated at 11.4 μg/mL (<5.0). The prothrombin time and activated partial thromboplastin time were 12.7 s (normal 10.5–13.5) and 38.7 s (26.1–35.8), respectively. Serum haptoglobin was not decreased at 211.9 mg/
Platelet-associated immunoglobulin G was 70 ng/10^7 cells (normal < 46). Serum complement C3 and C4 were not decreased at 111.2 mg/dL (normal 73–138), and 34.3 mg/dL (11–31), respectively. Hep-2 antinuclear antibody was negative. Anti-dsDNA, anti-Smith, anti-RNP, anti-SS-A, anti-SS-B, anti-topoisomerase I, and anti-centromere were all negative. Serum Epstein–Barr virus (EBV) markers were positive for viral capsid antigen (VCA)-IgG and EBV nuclear antigen-IgG, but negative for VCA-IgM and early antigen-IgG, suggesting latent EBV infection. There was no serological evidence of current or reactivated human immunodeficiency virus, hepatitis B or C, herpes simplex virus, or cytomegalovirus infection. Interferon-gamma release assay for tuberculosis was negative. Urinalysis was negative for proteinuria and occult blood.

Computed tomography revealed mild splenomegaly and small pleural effusion bilaterally, but no significant lymphadenopathy. There was no evidence of worsening of respiratory conditions such as interstitial pneumonia. Bone marrow aspiration cytology revealed activated macrophages and hemophagocytic cells but no malignant cells (Figure 2). A diagnosis of HPS was made on the basis of the clinicopathological findings.

The patient was treated with intravenous methylprednisolone 1 g/day and cyclosporine 200 mg/day. However, three days later, laboratory tests revealed a marked elevation of serum LDH (708 IU/L) and ferritin (16,632 ng/mL) with a decrease of platelet count of 1.5 × 10^4/μL. Since skin findings suggested rickettsiosis as a possible underlying cause of HPS, she was started on intravenous minocycline 200 mg/day with oral prednisolone 60 mg/day. The fever resolved and her general condition improved dramatically on the following day. The serum LDH and ferritin also improved rapidly. The patient received cyclosporine for four days, minocycline for 12 days, and prednisolone for 23 days.

In the course of her recovery, we received a report that the polymerase chain reaction (PCR) assay for O. tsutsugamushi (the Karp strain) was positive. PCR assays for Rickettsia japonica and bunyavirus-associated severe fever with thrombocytopenia syndrome were negative. Paired sera samples collected 16 days apart showed a four-fold increase in IgG and a 16-fold increase in IgM against the Karp strain of O. tsutsugamushi. The patient recovered and was discharged from hospital on day 45. The patient remains well 18 months later.

3. Discussion

Scrub typhus (also known as Tsutsugamushi disease) is a mite-borne infectious disease caused by O. tsutsugamushi (previously named Rickettsia tsutsugamushi). This disease has been mainly reported in East and Southeast Asia and in the northern regions in Australia [1]. This disease is most common in rural areas. Our patient lived in the rural area and also had been engaged in agriculture as the main occupation. Scrub typhus is associated with nonspecific symptoms, including fever, headache, cough, myalgia, and rash. The rash occurs in about one half of all patients and spreads from the trunk to the extremities; this rash was present in our patient. At the site of the infecting chigger bite, a papule often appears and then turns to a characteristic

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**Figure 1.** Photograph showing a pathognomonic skin ulcer (8 × 8 mm) on the right buttock, which was initially covered with black eschar.

**Figure 2.** Bone marrow aspiration cytology shows marked phagocytosis of leukocytes, platelets (A), and erythroblasts (B).
eschar with a thick black crust. Although eschar is the pathognomonic feature of scrub typhus, reports of its frequency in patients with the disease are highly variable (7–80%) [1]. This feature might be overlooked without careful examination of the skin. In our case, the bite, which developed into a skin ulcer, was located on the buttock (Figure 1).

Laboratory findings that confirm a diagnosis of scrub typhus include blood PCR and an indirect immunofluorescence antibody (IFA) assay using paired serum samples obtained at least two weeks apart. It is reported that the IFA assay needs to show at least a four-fold increase in IgG titer in paired samples from patients for a conclusive diagnosis of scrub typhus infection [2]. In our case, the IFA assay indicated a 4–16-fold increase in IgG and IgM titers in paired samples. Furthermore, PCR was positive for O. tsutsugamushi. As mentioned above, we received the IFA assay and PCR reports when the patient was recovering. A delay in starting antimicrobial therapy in our case might have led to serious complications or even death. A trial of antimicrobial therapy should be started empirically when there is a clinical suspicion of scrub typhus infection.

Our patient is the fourth Japanese case of scrub typhus infection-related HPS reported in the English-language literature to date. The case reports and case series published between 1994 and 2016 include 22 patients with scrub typhus who developed HPS (11 cases in China, 5 in India, 4 in Japan, and 1 case each in Korea and Australia) [3–14]. It has been reported that patients treated with appropriate antibiotics become afebrile within a few days and recover well from this disease. However, 3 (14%) of the 22 reported cases proved fatal despite administration of appropriate antibiotics. Our patient was treated with not only minocycline but also immunosuppressants, including corticosteroids (for 23 days) and cyclosporine (for 4 days). Eight (36%) of the 22 reported cases (including one that was fatal) were treated with immunosuppressants; however, 14 (64%) of the cases (including 2 that were fatal) did not receive immunosuppressants. Therefore, use of immunosuppressants does not appear to affect the risk of mortality in patients with this disease, and the need for immunosuppressants in patients with this disease remains unclear.

Scrub typhus infection may present with a number of non-specific clinical signs and symptoms. Furthermore, there is no clinical difference in HPS in association with scrub typhus infection and other causes, except the presence of eschar. The present case highlights the need to keep this scrub typhus in mind as one of the underlying diseases that may cause HPS, especially in patients living in East or Southeast Asia and Australia and those who have recently returned from endemic areas.

**Disclosure statement**

No potential conflict of interest was reported by the authors.

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