Case Report

A case report of tsutsugamushi disease mimicking disseminated *Bartonella* infection

Yu Yamamoto, Shigehiro Kuroki, Eiji Kajii

Abstract

We report the case of an 80-year-old man with tsutsugamushi disease who did not develop a typical eschar, but had a past history of cat bite and signs and symptoms mimicking disseminated *Bartonella* infection. He was hospitalized for fever, malaise, and skin rash after being bitten by a stray cat 2 weeks prior to admission. Initially, the patient was clinically diagnosed with severe *Bartonella* infection and treated with azithromycin, but he only defervesced the following day. Because of the presence of a maculopapular rash, elevated liver enzymes, and a partial response to azithromycin, a diagnosis of tsutsugamushi disease was considered, although no eschar was found after repeated meticulous physical examinations. Tsutsugamushi disease was confirmed by serological testing, and the patient was successfully treated with minocycline. This disease should be considered in endemic areas when a patient presents with fever and diffuse skin rash, even in the absence of a typical eschar on physical examination.

(Key words: tsutsugamushi disease, eschar, *Bartonella*, azithromycin)

Introduction

Tsutsugamushi disease is a mite-borne, acute febrile infectious disease caused by *Orientia tsutsugamushi*, an organism that is distributed throughout the Asian Pacific rim[1]. Clinical manifestations include a high-grade fever, headache, lymphadenopathy, skin rash, and a typical eschar. An eschar is the most important sign for early diagnosis because tsutsugamushi disease can be fatal if diagnosis and appropriate treatment are delayed[2]. Here, we report the case of a patient with tsutsugamushi disease who did not develop a typical eschar, thus mimicking disseminated *Bartonella* infection.

Case Report

An 80-year-old man without a significant past medical history was admitted to Wakuya national health insurance hospital in Miyagi prefecture for fever and malaise in late December. He had been in good health 2 weeks before admission, when he was bitten on the right index finger by a stray cat. Following the bite, he developed swelling, erythema, and pain around the bite wound, which spontaneously resolved within a few days. Three days before admission, he developed general malaise, fever, and a mild headache. His symptoms progressed, and he was hospitalized for further examination and treatment.

Division of General Medicine, Department of Community and Family Medicine, Jichi Medical University

He had no significant past medical history except for Weil's disease at 49 years of age. He was not under any medication and had never used illicit drugs. He was a farmer who worked in the fields and did not go into forests or mountains. He lived alone in Wakuya town of Miyagi prefecture in the Tohoku region of Japan and had not travelled recently. He drank alcohol socially and had a 60 pack-year history of smoking.

He appeared tired and anxious on physical examination. His temperature was 38.8℃, blood pressure 118/60 mmHg, pulse 96/min, respiratory rate 20/min, and oxygen saturation 93% on ambient air. A puncture wound was visible on the right index finger with surrounding purplish erythema (Fig. 1), and non-pruritic maculopapular rashes were found on his back and abdomen (Fig. 2). No typical eschar was found despite meticulous dermatological examination. Bilateral non-tender cervical lymphadenopathy was observed with a maximum diameter of 10 mm. Auscultation of the chest revealed bilateral diffuse fine crackles during inspiration. The rest of the examination was normal.

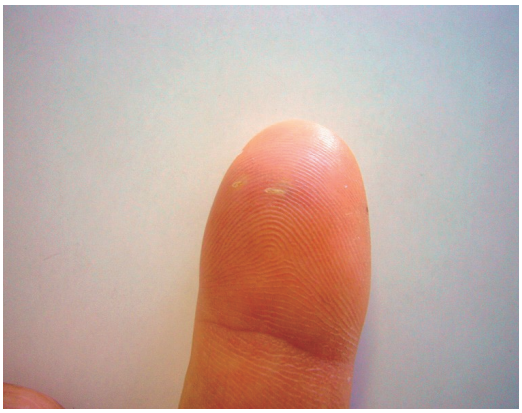

Figure 1. A puncture wound with surrounding purplish erythema on the right index finger following a stray cat bite.

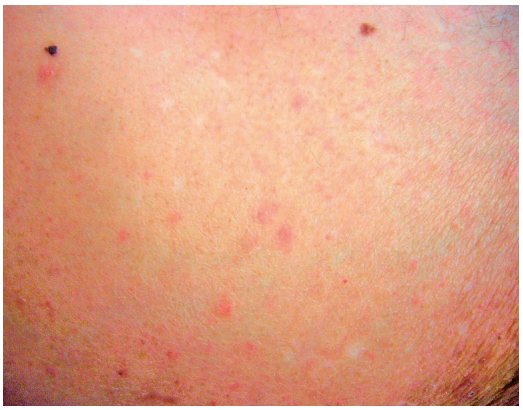

Figure 2. A maculopapular rash on the abdomen seen on day 1 of hospitalization.

Laboratory studies revealed a white blood cell count of 1,800 / μL with 85.6% neutrophils, 9.9g/dL hemoglobin, a platelet count of 48,000 / μL, 160 IU/L aspartate aminotransferase, 108 IU/L alanine aminotransferase, 547 IU/L lactate dehydrogenase, 2,154 IU/L creatine kinase, 26.5 mg/dL urea nitrogen, 0.9 mg/dL creatinine, 9.1 mg/dL C-reactive protein, and an erythrocyte sedimentation rate of 20 mm/h. His D-dimer level was high (24.2 μg/mL), but prothrombin and activated partial thromboplastin time were normal. His chest X-ray and computed tomography scan demonstrated increased interstitial infiltration in both lung fields.

Based on the history of a stray cat bite and the patient's clinical manifestations, we suspected disseminated *Bartonella* infection to be the most likely diagnosis. *Staphylococcus, Streptococcus, Pasteurella*, and other gram-negative bacillus were considered as possible pathogens, together with hematological disorders such as leukemia, lymphoma, and hemophagocytic syndrome. We performed a *Bartonella* antibody study and collected two sets of blood culture and a bone-marrow specimen. The patient was treated for disseminated *Bartonella* infection with 500 mg oral azithromycin on day 2 of

hospitalization followed by 250 mg daily for 4 days. He was afebrile on day 3, but his temperature rose again and reached 40.2℃ on day 5. Both sets of blood culture were negative, and no malignant cells or hemophagocytosis were found in the bone marrow specimen, even though it was hypoplastic. Azithromycin was discontinued on day 6, and intravenous ceftriaxone (2 g/day) and gentamicin (3 mg/kg/day) were administered for treating culture-negative severe *Bartonella* infection. Despite the absence of a typical eschar, we also considered tsutsugamushi disease, which is endemic in the Tohoku region and can cause a maculopapular rash, pancytopenia, and acute interstitial pneumonia. Treatment with oral minocycline hydrochloride (200 mg/day) for tsutsugamushi disease was simultaneously begun. After the change in antibiotics, his fever began to subside on day 8, and he was afebrile on day 10. As the fever subsided, pancytopenia and interstitial pneumonia gradually improved. Serological tests performed at SRL, Inc. (a clinical testing laboratory) using an indirect immunofluorescence antibody (IFA) technique against Kato, Karp, and Gilliam strains of *Orientia tsutsugamushi* were positive for anti-Gilliam strain IgM on day 9 of hospitalization. IFA titers of IgM and IgG against both Karp and Gilliam strains significantly increased on day 26 (Table 1). In contrast, anti-*Bartonella henselae* IgM was negative and IgG was positive in the serum sample on day 2. Gentamicin was discontinued on day 12 due to nausea, and treatment with ceftriaxone and minocycline hydrochloride was continued until day 32. After rehabilitation for disuse muscle atrophy, he was discharged without further sequelae.

	Strains		IFA titer on	
			Day 9	Day26
O.tsutsugamushi	Kato	IgM	10	10
		IgG	640	640
	Karp	IgM	10	40
		IgG	160	640
	Gilliam	IgM	160	1280
		IgG	320	2560

Table 1. Serological test results (indirect immunofluorescence antibody (IFA) technique).

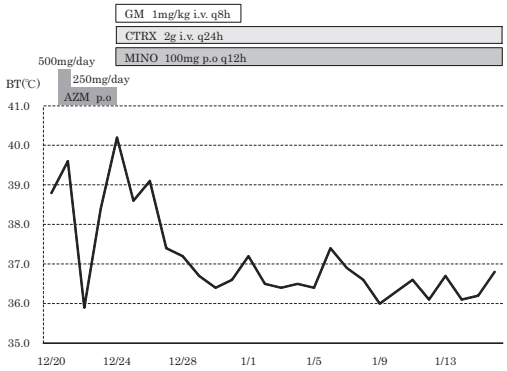

Figure 3. Clinical course.

Discussion

Tsutsugamushi disease is an acute febrile disease caused by *Orientia tsutsugamushi*, and is transmitted to humans through the bite of larval trombiculid mites of the genus *Leptotrombidium*. This disease is endemic in Asia and the Western Pacific region[1], and causes vasculitis or perivasculitis of the small blood vessels, resulting in severe complications such as respiratory complications[1, 3], acute renal failure[4], and coagulopathy[5]. This life-threatening disease is found even in developed countries, therefore early diagnosis and appropriate antibiotic treatment are essential[2]. It is endemic in Japan, where the total incidence from 2006–2009 was reported to be 1,705 by the Infectious Disease Surveillance Center of Japan. Tsutsugamushi disease occurs both in spring and early winter in the Tohoku-Hokuriku area,

whereas it occurs in early winter in other areas. This regional difference in patterns of occurrence arises from differences in the vector species and their geographical distribution[5].

Although serological testing using the IFA technique is slow, it is the preferred diagnostic tool for tsutsugamushi disease; therefore, it should be carried out as soon as this disease is considered in an acutely febrile patient to avoid delay in diagnosis. In this patient, tsutsugamushi disease was confirmed by IgM positivity for the Gilliam strain on day 9 and the significant increase in IgM and IgG titers against both Karp and Gilliam strains on day 26. Although IgM titers peak out within 2–3 weeks under the normal immune response, IgM against the Gilliam strain was still high in this patient on day 26. Because of his immunocompetence, his IgM titer may have been greater than 1: 1,280 if it had been evaluated a week earlier.

Because clinical manifestations and laboratory findings of tsutsugamushi disease are non-specific, its inclusion in the differential diagnosis of an acute febrile disease in endemic areas and the detection of a typical eschar (the single most useful diagnostic sign) are indispensable for early diagnosis. In addition, knowledge of the preferential areas in which eschars occur can simplify its diagnosis[6]. Because an eschar may be located in hidden areas such as the genital region or axilla, which are difficult to examine[1], careful and repetitive generalized dermatological examinations are required. The reported frequency of eschars in patients with tsutsugamushi disease is variable (46–100%)[6-9], which explains why a typical eschar may not be detected even after meticulous physical examination in some cases. In endemic areas, integration of tsutsugamushi disease with other clinical manifestations should be considered even when no eschars are found.

In addition to the absence of an eschar, our difficulty in diagnosing tsutsugamushi disease was exacerbated by the partial effectiveness of azithromycin, which was administered as an empirical therapy for disseminated *Bartonella* infection. Tetracyclines (doxycycline and minocycline) are the preferred treatment of choice for tsutsugamushi disease[10], although doxycycline resistance has been reported[11]. Successful treatment of this disease with azithromycin has been reported in pregnant women for whom tetracyclines are contraindicated[12]. Because some data show that various doses of azithromycin are as effective as tetracycline, azithromycin may be an appropriate alternative treatment for this disease[13, 14]. An increased dose of azithromycin may have led to successful treatment of this patient, even though he had severe tsutsugamushi disease with interstitial pneumonia and disseminated intravascular coagulation.

In conclusion, we report the case of a patient with tsutsugamushi disease who did not develop a typical eschar but had a history of cat bite and clinical manifestations mimicking disseminated *Bartonella* infection. Tsutsugamushi disease must be considered in the differential diagnosis of acute febrile disease with skin rash in endemic areas such as Japan to enable early treatment with appropriate antibiotics.

We are indebted to Harumi Yano and Alan Lefor for critical reading of the manuscript.

References

1. Watt G, Parola P: Scrub typhus and tropical rickettsioses. Curr Opin Infect Dis 16: 429-436, 2003.
2. Yasunaga H, Horiguchi H, Kuwabara K, et al.: Delay in tetracycline treatment increases the risk of complications in Tsutsugamushi disease: data from the Japanese Diagnosis Procedure Combination database. Intern Med 50(1): 37-42, 2011.

3. Wang CC, Liu SF, Liu JW, et al.: Acute respiratory distress syndrome in scrub typhus. Am J Trop Med Hyg 76(6): 1148-1152, 2007.
4. Kim DM, Kang DW, Kim JO, et al.: Acute renal failure due to acute tubular necrosis caused by direct invasion of *Orientia tsutsugamushi*. J Clin Microbiol 46: 1548-1550, 2008.
5. Ogawa M: Scrub typhus in Japan. Epidemiological and clinical features of cases reported in 1998. Am J Trop Med Hyg 67: 162-165, 2002.
6. Kim DM, Won KJ, Park CY, et al.: Distribution of eschars on the body of scrub typhus patients: a prospective study. Am J Trop Med Hyg 76(5): 806-809, 2007.
7. Berman SJ, Kundin WD: Scrub typhus in South Vietnam: A study of 87 cases. Ann Intern Med 79(1): 26-30, 1973.
8. Kawamura AJ, Tanaka H, Tamura A: Tsutsugamushi disease: Tokyo. University of Tokyo Press, 1995.
9. Ogawa M, Hagiwara T, Kishimoto T, et al.: Tsutsugamushi disease (scrub typhus) in Japan: epidemiological aspects. Kansenshogaku Zasshi 75(5): 353-358, 2001 (in Japanese, Abstract English).
10. Panpanich R, Garner P: Antibiotics for treating scrub typhus. Cochrane Database Syst Rev 4, 2009.
11. Watt G, Chouriyagune C, Ruangweerayud R, et al.: Scrub typhus infections poorly responsive to antibiotics in northern Thailand. Lancet 348(9020): b86-89, 1996.
12. Kim YS, Lee HJ, Chang M, et al.: Scrub typhus during pregnancy and its treatment: a case series and review of the literature. Am J Trop Med Hyg 75(5): 955-959, 2006.
13. Phimda K, Hoontrakul S, Suttinont C, et al.: Doxycycline versus azithromycin for treatment of leptospirosis and scrub typhus. Antimicrob Agents Chemother 51(9): 3259-3263, 2007.
14. Kim YS, Yun HJ, Shim SK, et al.: A comparative trial of a single dose of azithromycin versus doxycycline for the treatment of mild scrub typhus. Clin Infect Dis 39: 1329-1335, 2004.

播種性バルトネラ感染症と鑑別困難であったツツガムシ病の１例

山本　　祐，黒木　茂広，梶井　英治

要　約

猫咬傷の病歴と臨床徴候およびアジスロマイシンの部分的有効性から，播種性バルトネラ感染症と鑑別が困難であった特徴的刺し口を欠くツツガムシ病の１例を報告する。患者は80歳男性。野良猫に右示指を咬まれた約２週間後に発熱，全身倦怠感および皮疹をきたしたため受診し，精査加療目的に入院した。臨床的に重症バルトネラ感染症と診断してアジスロマイシン投与による治療を開始し，翌日は無熱となるものの治療３日目には高熱の再燃を認めた。繰り返す詳細な身体診察においても特徴的刺し口を発見できなかったが，発熱に加え斑状丘疹と肝逸脱酵素上昇を伴い，アジスロマイシンが部分的に有効性であったことからツツガムシ病を疑った。ミノサイクリン投与で合併症なく治癒し，血清学的にツツガムシ病の確定診断を得た。ツツガムシ病流行地域における発疹性発熱患者診療の際は，特徴的な刺し口を欠いていた場合でもツツガムシ病を考慮すべきである。

自治医科大学地域医療学センター総合診療部門