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Case report

Scrub typhus mimicking the clinical course of infectious mononucleosis: a case report

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Abstract

Objective: Scrub typhus is a relatively common life-threating disease; its symptoms are non-specific and similar to those of other viral infections. Therefore, scrub typhus might be underdiagnosed.
Patient: Herein, we report a patient with scrub typhus whose clinical course mimicked that of infectious mononucleosis. A 63-year-old male patient with hypertension presented to our hospital complaining of symptoms including prolonged fever, pharyngeal discomfort, and a mild headache. He showed the appearance of a rash after amoxicillin administration. At the same time, he did not show a crusted rash on his body surface.
Results: After a comprehensive examination, Epstein-Barr virus and cytomegalovirus infections were ruled out. We suspected that this patient suffered from scrub typhus on the basis of his usual lifestyle. Finally, polymerase chain reaction analysis showed a positive result for deoxyribonucleic acid of *Orientia tsutsugamushi* in his blood sample. Fortunately, he recovered naturally with only supportive treatment during his hospitalization.
Conclusion: We should observe and monitor patients with infectious mononucleosis-like symptoms and emphasize the importance of a clinical interview.

Key words: scrub typhus, *Orientia tsutsugamushi*, infectious mononucleosis

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Introduction

Scrub typhus a life-threatening disease which is relatively common and every physician might come across it in multiple settings[1]. It is caused by the infection of *Orientia tsutsugamushi* and is characterized by fever, headache, myalgia, and vomiting. Half of the patients with scrub typhus show an eschar and a spotted rash[1]. Scrub typhus is occasionally complicated with the presence of encephalitis, respiratory failure, and disseminated intravascular coagulation (DIC), which could finally lead to mortality[1, 2]. However, early appropriate treatment including antibiotics like tetracycline could improve the prognoses of patients with scrub typhus[3]. Generally, the isolation of *Orientia tsutsugamushi* in culture is definitive. Additionally, antibodies of paired sera obtained at least two weeks apart are necessary for serological confirmation. The diagnosis by detecting the presence of a ≥4-fold rise in titer, in spite of causing a delay in confirmation, gives clear results. Hence, polymerase chain reaction (PCR) assay is a useful and prompt diagnostic tool to detect the deoxyribonucleic acid (DNA) of *Orientia tsutsugamushi* in the blood or crust samples of a patient (sensitivity, 86.5%; specificity, 100%)[4, 5]. Consequently, if we suspect that a patient suffers from scrub typhus, we should not await the results of IgM antibodies and PCR assays; instead, we should administer antibiotics. In our patient, it was difficult to diagnose scrub typhus as we could not find a stab with a crust[6] and the patient could not recollect any outdoor activities performed by him. Fortunately, our patient's condition improved naturally with symptomatic treatment in the hospital. We present a case with scrub typhus mimicking the clinical course of infectious mononucleosis (IM).

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Case report

A 63-year-old male patient with hypertension presented to our hospital complaining of symptoms including prolonged fever, pharyngeal discomfort, and a mild headache for which no antibiotic provided relief. Furthermore, he was prescribed amoxicillin hydrate (AMPC) at another clinic, after the ingestion of which a sporadic rash appeared on his body. His blood pressure, heart rate, body temperature, and respiratory rate were 144/82 mmHg, 92 beats/min, 38.2°C, and 18 breaths/min, respectively. His physical examination revealed a spotted rash over his whole body (Figure 1) and also lymphadenopathy affecting the cervical, axillary, and inguinal lymph nodes; meanwhile, crusts did not appear on his body surface. A blood analysis showed elevations of C-reactive protein (7.69 mg/dL) and liver enzyme levels including aspartate transaminase (83 U/L) and alanine aminotransferase (97 U/L) (Table 1). Moreover, a complete blood count analysis showed a slightly increased white blood cell count (10,420 /μl) with atypical lymphocytes and mild thrombocytopenia (10.9 $\times 10^4$/μl) (Table 1). A computed tomographic (CT) scan showed a slight splenomegaly but no evidence of a focal infection (Figure 2). Initially, we diagnosed him with IM, because the development of a sporadic rash after the administration of AMPC, an increased white blood cell count with atypical lymphocytes, elevation of liver enzymes, lymphadenopathy, and splenomegaly on CT scan indicate a clinical course of IM. However, we hospitalized him for supportive treatment and further examination of the fever that lasted approximately 7 days. After hospitalization, we prescribed non-steroidal anti-inflammatory drugs to him for his headache. Furthermore, a lumbar puncture showed an increase in white cell count (69/mm^3) and an elevation in protein levels (62.3 mg/dL) in the cerebrospinal fluid without evidence of bacterial meningitis, which suggested the presence of aseptic meningitis. However, as his general appearance was good, we followed him up with close observation without administering antibiotics. Finally, his blood analysis revealed negative results for hepatitis A, B, and C, tuberculosis, influenza, human immunodeficiency virus, and human T-cell leukemia virus-1 infections, and also for past infection patterns of Epstein-Barr virus and cytomegalovirus (Table 1). Autoantibodies testing, including that for anti-nuclear antibody, did not show significant results (Table 1). Although he denied an obvious episode of outdoor activities and bug bites at first, he confessed later

Figure 1 A spotted rash on the patient's right femoral skin; It appeared after administration of amoxicillin hydrate; it did show a tendency to fuse and was not painful and itchy. It almost disappeared at day 11.

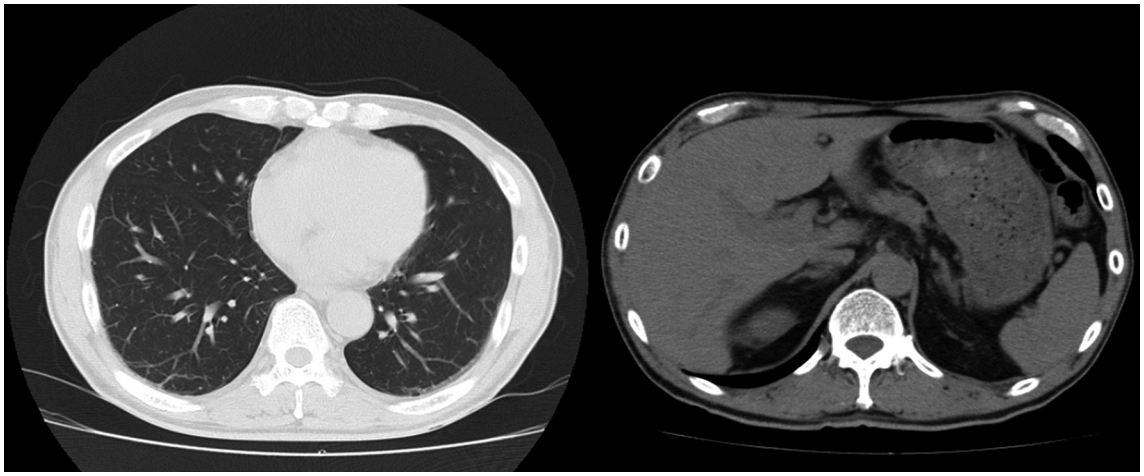

Figure 2 Computed tomographic images of the lung; image on the left side is the lung field condition that shows no pneumonia and pleural effusion. Image on the right side shows mild splenomegaly and no evidence of bacterial infection in organs.

Table 1 Laboratory data on admission

Hematology	White blood cell	10,420 /μL
	Neutrophil	8,336 /μL
	Atypical lymphocyte	4%
	Hemoglobin	16.3 g/dL
	Platelet	10.9 ×10^4/μL
Biochemistry	Total protein	7.9 g/dL
	Albumin	4.1 g/dL
	AST	83 U/L
	ALT	97 U/L
	Total Bilirubin	0.9 mg/dL
	γ-GTP	93 U/L
	LDH	468 U/L
	CPK	46 U/L
	Glucose	174 mg/dL
	BUN	21.3 mg/dL
	Creatinine	0.81 mg/dL
	Na	131 mEq/L
	K	4.1 mEq/L
	C reactive protein	7.69 mg/dL
	Ferritin	875.7 ng/mL
	sIL-2 receptor	2,370 U/mL
	CEA	4.0 ng/mL
	CA19-9	22.2 U/mL
Blood coagulation test	PT-INR	0.96
	APTT	38.5 seconds
	D-dimer	10.1 μg/ml
Antigen antibody test	HBs antigen	Negative
	HBc antibody IgG	Negative
	HCV antibody	Negative
	IgA-HEV antibody	Negative
	IgM-HA	Negative
	EBV VCA IgM	Negative
	EBV EBNA IgG	Positive
	EBV EA IgG	Negative
	CMV IgM	Negative
	CMV IgG	Positive
	HIV antigen antibody	Negative
	Antinuclear antibody	1:40
	Rheumatoid factor	7 IU/mL
	PR3-ANCA	< 1.0 U/mL
	MPO-ANCA	< 1.0 IU/mL
	TB specific IFN γ	Negative
Influenza A		Negative
Influenza B		Negative

AST: aspartate transaminase; ALT: alanine aminotransferase; APTT: activated partial thromboplastin time; γ-GTP: γ-glutamyltransferase; LDH: lactate dehydrogenase; CPK: creatine phosphokinase; BUN: blood urea nitrogen; sIL-2 receptor: soluble interleukin-2 receptor; CEA: carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9; HBs: hepatitis B surface; HBc: hepatitis B core; HCV: hepatitis C virus; HEV: hepatitis E virus; HA: hepatitis A virus; EBV VCA IgM: Epstein-Barr virus-viral capsid antigen antibody, immunogloblin M; EBV EBNA IgG: Epstein-Barr virus- Epstein-Barr virus nuclear antigen, immunogloblin G; EBV EA IgG: Epstein-Barr virus-early antigen, immunogloblin G; CMV: cytomegalovirus; HIV: human Immunodeficiency Virus; PR3-ANCA: proteinase-3-anti-neutrophil cytoplasmic antibody; PT-INR: prothrombin time-international normalized ratio; MPO-ANCA: myeloperoxidase-anti-neutrophil cytoplasmic antibody; TB specific IFN γ: Mycobacterium Tuberculosis specific interferon gamma.

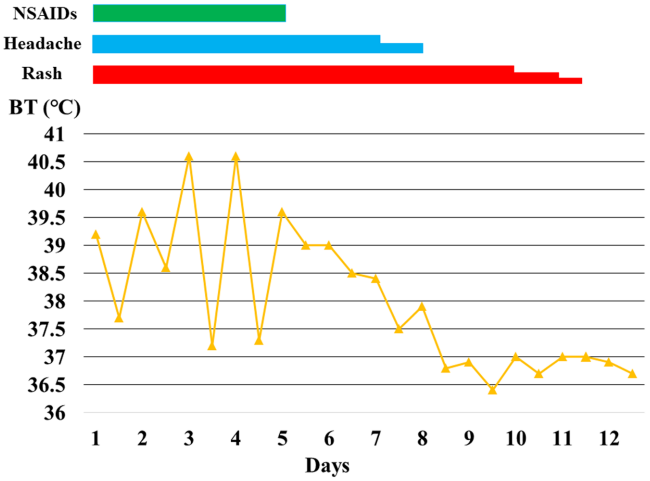

Figure 3 Clinical course of this case during hospitalization; the patient's main symptoms were headache and rash which improved with a drop in his fever. Until day 5, he took non-steroidal anti-inflammatory drugs as needed, but he did not require them after that. He was discharged on day 12 without complications.

Table 2 Serological test results [immunofluorescence antibody (FA) technique and polymerase chain reaction (PCR)]

	Strains		FA titer Day 5
Orientia tsutsugamushi	Kato	IgM	640
		IgG	640
	Karp	IgM	640
		IgG	1280
	Gilliam	IgM	640
		IgG	640
PCR	Type		Result
Orientia tsutsugamushi	Karp		Positive
Rickettsia japonica			Negative

that he often used to walk along the bank before the onset of fever. Therefore, we suspected that he suffered from scrub typhus and, therefore, we conducted a PCR assay and an IgM antibodies assay by the fluorescent antibody method (FA) to detect *Orientia tsutsugamushi*. His clinical condition improved naturally with only supportive treatment at that time; therefore, he was not administered antibiotics in his hospitalization period (Figure 3). He was discharged without a complication. Finally, we obtained a positive result for *Orientia tsutsugamushi* (Karp type) with the PCR assay and an IgM assay by FA when he visited the hospital as an outpatient (Table 2), and we diagnosed him with scrub typhus. Fortunately, he did not have a relapse and complications for more than two months after discharge.

Written informed consent was obtained from the patient for the publication of this case report and any accompanying images.

Discussion

Scrub typhus is a potentially life-threatening disease complicated severely by encephalitis, respiratory failure, and DIC[1, 2]. Symptoms of scrub typhus are relatively non-specific and mimic viral infections like IM. However, its diagnosis is relatively easy when a patient has been involved in outdoor activities and/or shows a classical stab with a crust, which appears in half of the patients with scrub typhus. Conversely, it might go underdiagnosed especially when a patient with scrub typhus does not display a classical stab with a crust[6]. Moreover, even if a patient with scrub typhus does not remember an obvious episode of outdoor activities, living in rural areas is a risk factor for the infection of scrub typhus[7] and, therefore, we should endeavor to detect stabs with a crust and conduct interviews to reveal the possibility of a tick bite. Simultaneously, we must endeavor to find stabs with a crust, especially in common but elusive body surfaces such as the axillae, genital areas, and intertriginous areas[1]. Although some patients with scrub typhus might recover naturally only with supportive treatment like in our case, it is essential to administer antibiotics to patients for improving their clinical condition[8]. Furthermore, we re-stress the importance of a detailed medical interview to diagnose scrub typhus for revealing the possibility of tick bite.

Classical scrub typhus transmitted by *Leptotrombidium akamushi* is prevalent during summer, but new types of scrub typhus transmitted by *Leptotrombidium scutellare* and *Leptotrombidium pallidum* are prevalent from spring to autumn[9, 10]. Previously, scrub typhus was prevalent in the Tohoku region in Japan, but recently it has been found to occur all over Japan except for the northern and southern regions. Therefore, it is a relatively common disease all over Japan; hence, it might remain underestimated. The pathophysiology of scrub typhus includes disseminated vasculitis involving several organs such as the skin, liver, brain, kidneys, meninges, and lungs. Occasionally, vascular injury causes DIC, pulmonary edema, shock, hepatic dysfunction, and meningoencephalitis[11]. Although recovery from the mild form of scrub typhus happens naturally, mortality may be as high as 24% in severe cases[1]. Additionally, symptoms of scrub typhus are non-specific and are partly similar to those of other viral infections including IM; these include prolonged fever, sore throat, rash, lymphadenopathy, liver dysfunction, hepatomegaly, and splenomegaly. Furthermore, we should refrain from prescribing antibiotics without evidence of a bacterial infection, because it might lead to a misdiagnosis, like in our case. On suspecting scrub typhus in a patient, we should evaluate IgM antibodies for *Orientia tsutsugamushi* and/or conduct a PCR assay to diagnose it and use antimicrobial agents including a tetracycline antibiotic without delay[1].

It might be difficult to diagnose scrub typhus in patients without a stab with a crust. Furthermore, the symptoms of scrub typhus are nonspecific like fever, headache, myalgia, cough, and digestive symptoms. Therefore, scrub typhus occasionally went underdiagnosed and resulted in mortality[8]. Although several diagnostic methods are available, if we do not consider scrub typhus as a differential diagnosis, we might underdiagnose it[12]. We should repeatedly interview patients about exposures to situations where tick bites could occur, because they may be unaware of events that could lead to scrub typhus. The key point of a medical interview should be to reveal whether a patient was exposed to an environment, such as a grassy place, where ticks could inhabit[7]. Hereby, we emphasize that a detailed medical interview is a crucial clinical technique, particularly while performing a differential diagnosis.

In summary, we should observe and monitor patients with IM-like symptoms, because a misdiagnosis could lead a patient with scrub typhus to mortality. Additionally, we should bear in mind that a detailed medical interview is a crucial clinical technique in the diagnosis of scrub typhus.

Conflict of interest: The authors declare no conflicts of interest in association with the present study.

References

1. Peter JV, Sudarsan TI, Prakash JA, *et al*. Severe scrub typhus infection: clinical features, diagnostic challenges and management. World J Crit Care Med 2015; 4: 244–250. [Medline] [CrossRef]
2. Rajapakse S, Weeratunga P, Sivayoganathan S, *et al*. Clinical manifestations of scrub typhus. Trans R Soc Trop Med Hyg 2017; 111: 43–54. [Medline] [CrossRef]
3. Wee I, Lo A, Rodrigo C. Drug treatment of scrub typhus: a systematic review and meta-analysis of controlled clinical trials. Trans R Soc Trop Med Hyg 2017; 111: 336–344. [Medline] [CrossRef]
4. Allen AC, Spitz S. A comparative study of the pathology of scrub typhus (Tsutsugamushi disease) and other rickettsial diseases. Am J Pathol 1945; 21: 603–681. [Medline]
5. Tantibhedhyangkul W, Wongsawat E, Silpasakorn S, *et al*. Use of multiplex real-time PCR to diagnose scrub typhus. J Clin Microbiol 2017; 55: 1377–1387.

[Medline] [CrossRef]
6. Premraj SS, Mayilananthi K, Krishnan D, *et al*. Clinical profile and risk factors associated with severe scrub typhus infection among non-ICU patients in semi-urban south India. J Vector Borne Dis 2018; 55: 47–51. [Medline] [CrossRef]
7. Kim S, Kim JS, Lee H. Epidemiological characteristics of scrub typhus in Korea, 2009. Osong Public Health Res Perspect 2010; 1: 55–60. [Medline] [CrossRef]
8. 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 2011; 50: 37–42. [Medline] [CrossRef]
9. Ebisawa I. Current epidemiology and treatment of Tsutsugamushi disease in Japan. J Travel Med 1995; 2: 218–220. [Medline] [CrossRef]
10. Ogawa M, Ono T. Epidemiological characteristics of tsutsugamushi disease in Oita Prefecture, Japan: yearly and monthly occurrences of its infections and serotypes of its causative agent, Orientia tsutsugamushi, during 1984–2005. Microbiol Immunol 2008; 52: 135–143. [Medline] [CrossRef]
11. Chrispal A, Boorugu H, Gopinath KG, *et al*. Scrub typhus: an unrecognized threat in South India—clinical profile and predictors of mortality. Trop Doct 2010; 40: 129–133. [Medline] [CrossRef]
12. Sando E, Suzuki M, Katoh S, *et al*. Distinguishing Japanese spotted fever and scrub typhus, central Japan, 2004–2015. Emerg Infect Dis 2018; 24: 1633–1641. [Medline] [CrossRef]