Case report

Title page

A case of scrub typhus complicated by severe DIC and death

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Running title: Scrub typhus with DIC and death

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Abstract and Key words

Abstract

Scrub typhus is an infectious disease that is caused by *Orientia tsutsugamushi*. The authors describe an autopsied case of scrub typhus complicated with severe DIC. An 82-year-old man complained of fever 4 days after climbing a mountain. The patient was admitted to an urban hospital, and meropenem and ceftriaxone were administered. The patient's condition deteriorated and he was transferred to a second hospital. On physical examination, a black scab was found and scrub typhus was suspected. Despite intensive treatment, the patient died on the 5th day. High levels of *O. tsutsugamushi* IgM antibody were confirmed. An autopsy revealed systemic vasculitis and perivasculitis. The endothelial tissue of the white pulp of the spleen was markedly infiltrated by plasma cells. The authors speculated that a severe immune reaction against *O. tsutsugamushi* enhanced an inflammatory response, leading to DIC. This case is a warning to doctors who are not familiar with scrub typhus.

(150 words)

Key words: acute renal failure, autopsy, DIC, *Orientia tsutsugamushi*, scrub typhus.

Introduction

Scrub typhus (Tsutsugamushi disease) is an infectious disease that is caused by *Orientia tsutsugamushi*. Following 5–14 days of incubation, symptoms such as fever, enlarging skin eruptions and lymph node enlargement occur. In typical cases, a black scab at a bite site is an important clue for early diagnosis. Although tetracycline is markedly effective, the mortality rate is 30% in cases of delayed treatment and the disease is complicated by renal failure, systemic inflammatory response syndrome (SIRS) and disseminated intravascular coagulation syndrome (DIC).[1,2]

The authors present a severe case of scrub typhus complicated with DIC in a patient who did not survive even with intensive care. This report describes important pathological characteristics of scrub typhus, which suggest histopathological mechanisms of SIRS and DIC.

Case report

An 82-year-old man climbed a mountain in April in Fukushima prefecture, in the northern part of Japan, to get edible wild plants. The patient complained of fever and general fatigue 4 days later. Although the patient was prescribed cefdinir by a local hospital, the symptoms did not improve, and 8 days after climbing, the patient was

admitted to an urban hospital because of a reddened swelling in the left thigh, steadily increasing in size. Cellulitis was diagnosed, and meropenem and ceftriaxone were administered. The patient's condition worsened and progressed to renal failure. On the 13th day, the patient was transferred to Fukushima Medical University Hospital because of severe septic shock of unknown cause.

On presentation, the patient's clinical condition was unstable (consciousness level: E3V2M5 (GCS), blood pressure: 78/48 mm Hg, respiratory rate: 18/min, body temperature: 37.6 °C), and a black scab was found on the left thigh (Fig. 1). Blood tests revealed metabolic acidosis (pH: 7.079, HCO_3^-: 11.1 mmol/L, base excess: -18.3 mmol/L), coagulopathy (platelet count: 4.5×10^7 cells/L, prothrombin time international normalized ratio (PT-INR): 1.93, activated partial thromboplastin time: 120.8 seconds, antithrombin III: 24%), and renal failure (blood urea nitrogen: 26.4 mmol/L, creatinine: 500 μmol/L). In the emergency room, the patient's consciousness level declined and was associated with generalized cramping. The authors performed emergency endotracheal intubation and admitted the patient to the ICU. Septic shock due to scrub typhus was strongly suspected based on the clinical history and characteristic black scab. High-dose minocycline (200 mg/day), gamma globulin (5000 mg/day), anti-thrombin (1500 units/day) and gabexate mesilate (29 mg/kg/day) were prescribed. Even with

intensive treatment, the authors could not prevent deterioration and multiple organ dysfunction. The authors noticed anisocoria on the 17th day, and cerebral haemorrhage was strongly suspected. However, the patient's general condition was too severe for transfer to the radiological department, and CT was thus not able to be performed. The patient died on the 18th day. High levels of tsutsugamushi IgM antibody (Kato: 1/2560 dilution, Karp: 1/2560 dilution, Gilliam: 1/1280 dilution) were confirmed in blood samples collected on admission. The patient's family accepted the authors' proposal of an autopsy and, with the collaboration of pathologists, the authors attempted to evaluate the pathological characteristics.

Pathological findings

The bite site and entry of *O. tsutsugamushi*, with epidermal ulceration covered by a black crust and surrounded by an erythematous halo, was found on the left thigh on gross examination. Histologically, the following was seen: marked necrosis of surface dermis and epidermis with severe septal panniculitis of the subcutaneous fatty tissue, accompanied by marked inflammatory cell infiltration consisting mostly of macrophages in the bite site. Vasculitis and perivasculitis were observed in several organs. Infiltration by plasma cells in the vascular endothelial tissue of the white pulp of

the spleen (175 g) was remarkable and induced slight stenosis of internal spaces (Fig. 2). Additionally, endocarditis was induced by infiltration of inflammatory cells. A section of the left ventricle was replaced with fibrous cicatrices due to previous myocardial infarction. In the liver (1150 g), spotted necrosis and diffuse vacuolar degeneration were observed in hepatic lobules. Marked oedema of both lungs (left: 440 g, right: 430 g) was found and was believed to be associated with scrub typhus and cardiac insufficiency. Accumulation of pericardial effusion (150 mL) was seen. Haemorrhage was found in the right cerebellopontine angle accompanied by diffuse subarachnoid haemorrhage in the brain stem and cerebrum (1530 g). Clinical symptoms indicated DIC; however, diffuse microvascular emboli in autopsied tissues were not found. The pathologists speculated that post-mortem fibrinolysis occurred, which is sometimes seen in autopsy cases.[3]

Discussion

Scrub typhus is induced by the organism *O. tsutsugamushi*, which belongs to the genus *Rickettsia*. Its occurrence is limited to East Asia, South Asia and Australia.[4,5] Three types of ticks (*Leptotrombidium akamushi*, *Leptotrombidium scutellare* and *Leptotrombidium pallidum*) transmit *O. tsutsugamushi*. In Japan, estimates of between

313 and 791 cases per year are diagnosed and result in 1–3 deaths.[6] An autopsy case is rare. Although tetracycline is markedly effective, acute renal failure, acute respiratory distress syndrome and DIC are complications of delayed treatment. Typical symptoms such as a black scab, enlarging skin eruptions and a typical clinical history were seen in this case.

Allen and Spitz[7] reported detailed pathological characteristics of scrub typhus in 1945. The report described a diffuse infiltration of lymphocytes, plasma cells or macrophages in multiple organs. The study predates the concepts of SIRS and DIC. However, the authors referred to a diffuse inflammatory vascular disorder in rickettsial infections.

It appears that there are several mechanisms involved in the development of DIC in scrub typhus. Past reports suggested that *O. tsutsugamushi* includes a toxin similar to an endotoxin, which damages vascular endothelial cells after infection. It causes microvascular proliferation and microvascular thrombus formation.[8] Proliferation of *O. tsutsugamushi* induces a systemic reduction of thrombomodulin levels and release of tissue necrosis factors. Cecilia and colleagues[8] reported that target cells of *O. tsutsugamushi* were endothelial cells in all major organs (heart, lung, brain, and kidney), cardiac muscle cells and macrophages located in liver and spleen. These findings were determined using an anti-Orientia immunohistochemical method. In this case,

remarkable autopsy findings were: severe infiltration of plasma cells in the vascular endothelial tissue of the white pulp of the spleen, endocarditis caused by infiltration of inflammatory cells, and systemic vasculitis and perivasculitis. It appears that DIC in scrub typhus is associated with endothelial cell damage and a systemic immune reaction. The authors speculate that a severe immune reaction against *O. tsutsugamushi* enhances a vascular inflammatory response and the development of DIC. Pathological findings in this case provide support for a histopathological mechanism of DIC in scrub typhus. Matsushita estimated that the risk of DIC clearly increases in cases of treatment delayed longer than 8 days after disease onset.[9] In this case, the first administration of minocycline was performed on the 13th day. The most important clinical factors in cases of scrub typhus are early diagnosis and treatment.

Conclusion

When scrub typhus is suspected based on clinical signs, peculiar bite site (black scab) or in the case of infections of unknown origin, appropriate and specific treatment (tetracycline) must be initiated as soon as possible. This case serves as a warning to doctors who are not familiar with scrub typhus. The essential aetiology of scrub typhus appears to be endothelial cell damage and systemic inflammatory response.

Competing interests

No conflicts of interest or industry relationships exist.

Acknowledgement

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Figure legends

Figure 1. Primary skin lesion

Primary skin lesion of the bite site and entry of *Orientia tsutsugamushi* on the left leg showing epidermal ulceration covered by a black crust surrounded by an erythematous halo.

Figure 2. Spleen

HE×400 Vasculitis of the spleen showing plasma cell infiltration in subendothelium of white pulp (arrows).

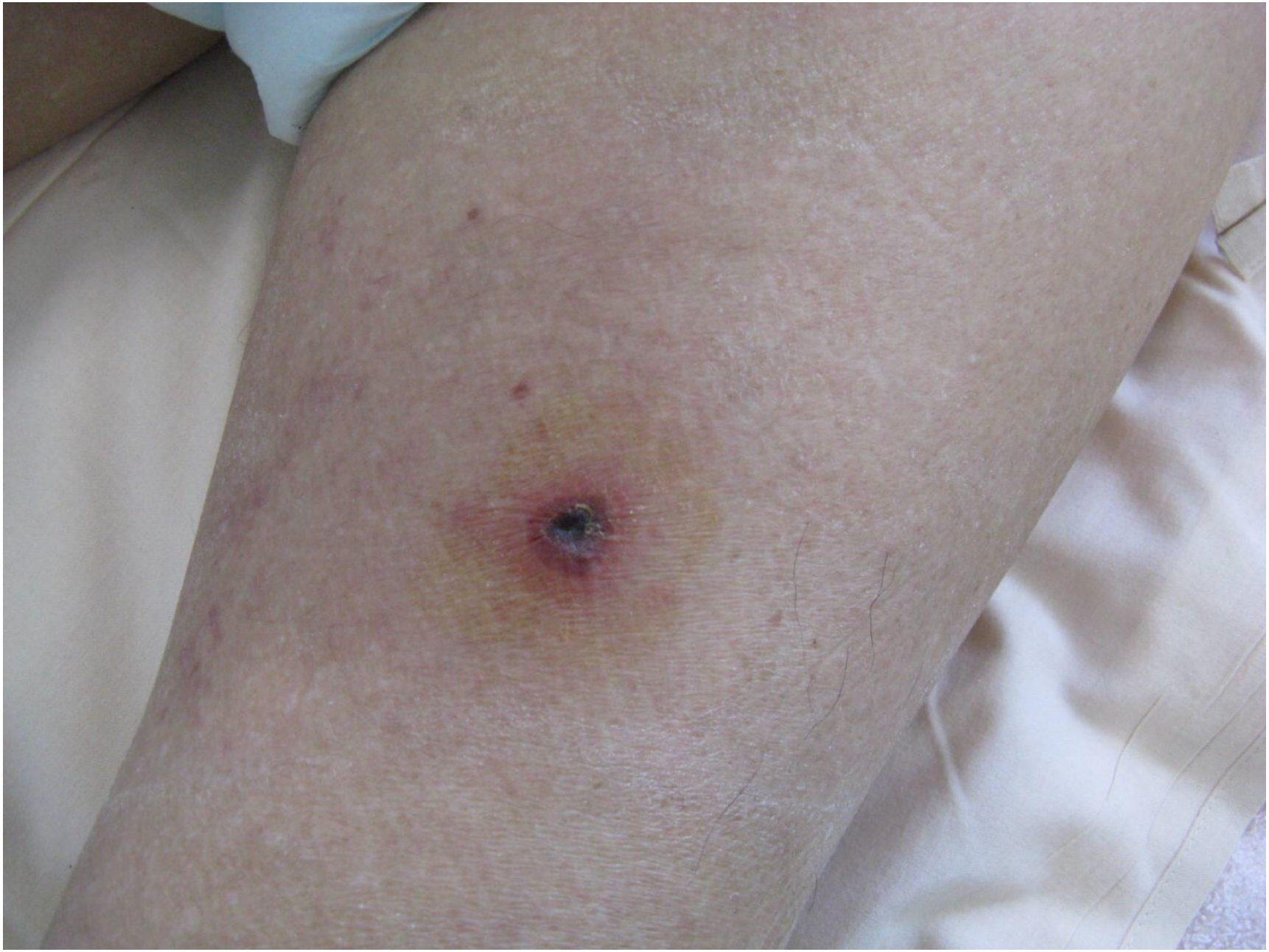

Figure1. Primary skin lesion

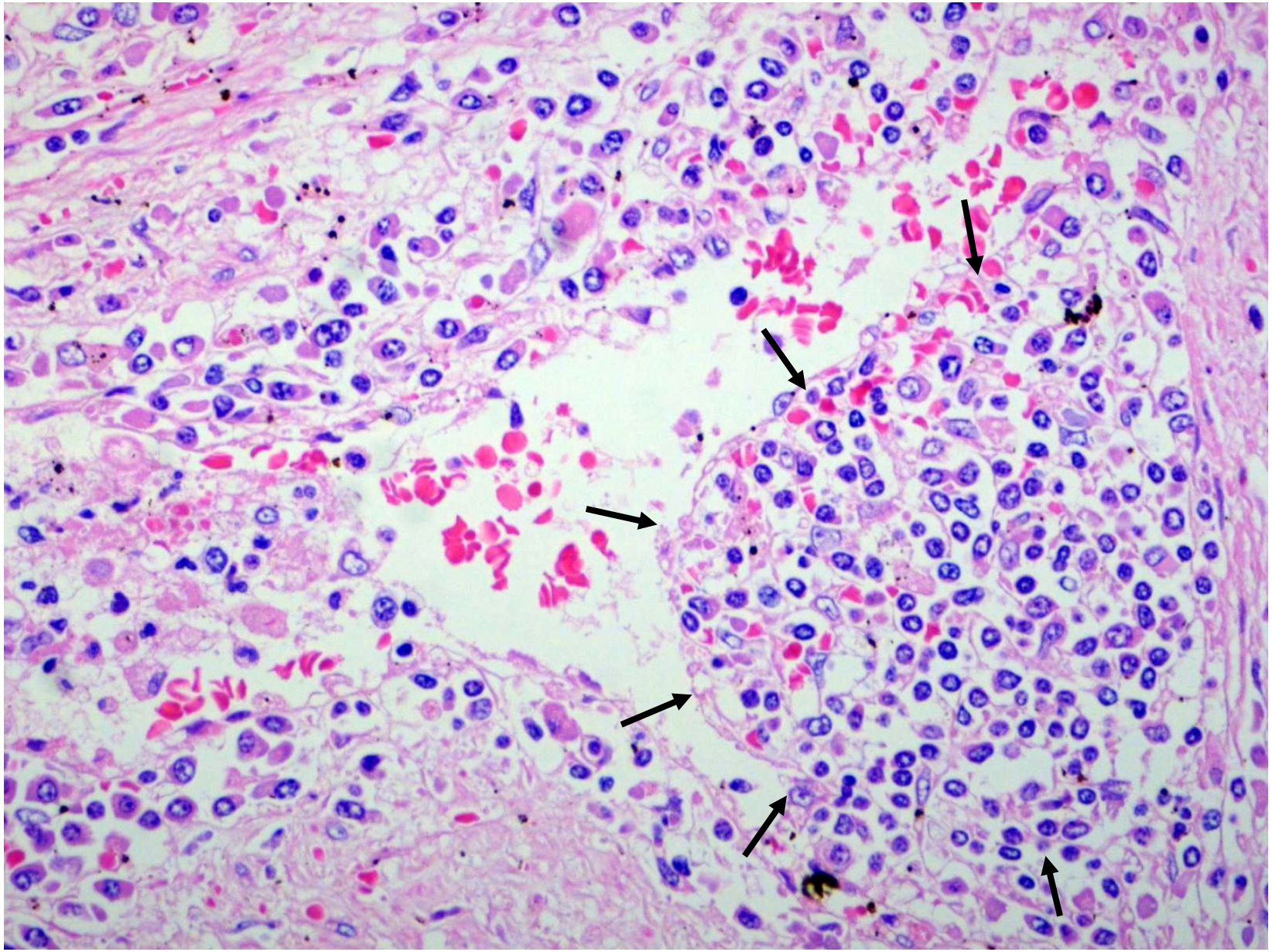

Figure 2 Spleen