American Journal of Clinical Microbiology and Antimicrobials

Review Article
Published: 02 Dec, 2019

Scrub Typhus in Japan

Takaaki Yoshimoto[1] and Taiji Yoshimoto[2]*

[1]*Department of Internal Medicine, Hitachi-Ota City Kegano Clinic, Japan*

[2]*Chief, Department of Gastroenterology, Musashino Tokushukai Hospital, Tokyo,Japan*

Abstract

Scrub typhus (Tsutsugamushi disease) is a zoonotic bacterial infection with three main clinical manifestations, fever, skin eruption, and eschar; a necrotic lesion of the skin presented at the site of an infected chigger bite, pathognomonic of scrub typhus. The World Health Organization (WHO) in 1999 stated that: scrub typhus is probably one of the most underdiagnosed and an underreported disease that often requires hospitalization. Scrub typhus is a serious health problem especially in the region known as Tsutsugamushi Triangle. Without appropriate treatment, the case fatality of scrub typhus can reach higher than 30% as a result of multi-organ failure. Scrub typhus is the most common rickettsial infection in Japan and was classified as fourth notifiable infectious disease in 1999. In this article, we review the history of scrub typhus in Japan, and provide new information, chief events and current status of epidemiology. For a better understanding of scrub typhus, a typical case of Tsutsugamushi disease was presented.

Keywords: Rickettsia; Scrub typhus; Eschar; Skin eruption; Tsutsugamushi triangle

Introduction

Scrub Typhus (ST), also called Tsutsugamushi disease in Japan, is an acute febrile disease caused by *Orientia tsutsugamushi*, an obligate intracellular gram-negative bacteria. In contrast to other *Rickettsia*, it has a different cell wall structure and genetic composition, possesses neither lipoprotein nor glycoprotein in cell wall [1]. Human are infected accidently by the bite of the larva (chigger) harbouring *O. tsutsugamushi*. The chigger attaches firmly to the surface of the host with the mouth parts (chelicerae) sucking up liquid tissue and the pathogens are transmitted to the people. Major serotypes of scrub typhus vary depending on different countries and endemic areas. Kato, Karp, Gilliam, Kuroki, Kawasaki and Shimokoshi are six main serotypes in Japan. They can be simply classified as akamushi (classical) and nonakamushi (new) serotypes of scrub typhus. Originally, the first 3 serotypes, Karp, Kato, and Gilliam were considered as major antigenic types, have been used as 3 prototypes for the clinical and experimental study of ST. However, many isolated *Orientia tsutsugamushi* strains, which are distinguishable from three prototype strains both in antigenicity and in virulence, have been reported in various parts of Asia (including Japan). New serotypes of Kuroki, Kawasaki, and Shimokoshi were isolated by Ohashi [2], Yamamoto [3] and Tamura [4] in 1990, 1989, and 1984 respectively. The strain of Kuroki of *O. tsutsugamushi* was isolated from a patient in Kyushu, Japan. Kawasaki serotype of ST was also isolated from a patient in Kyushu. Both Kawasaki and Kuroki are the most common serotypes of scrub typhus in recent years. The incidence of Shimokoshi serotype is very low (Shimokoshi was a family name of a 24 years old male lived in Niigata). Only few cases of this serotype were reported in northeastern Japan (Yamagata, Akita and Fukushima) following the first observation in Niigata prefecture. For a correct serological test, a total of six, 3 standards and 3 new serotypes (Kawasaki, Kuroki, and Shimokoshi if possible) should be employed for Indirect Immunofluorescent Antibody (IFA) and Indirect Immuno-Peroxidase (IIP) assay for a correct diagnosis of serotype of scrub typhus.

Brief Review of History of Scrub Typhus in Japan

Scrub typhus in Japan Honshu (Main Island)

The classical (serotype Kato) ST, transmitted by *Leptotrombidium akamushi* had been endemic before Second World War since early 1800s (Image 1). It occurred in summer (7th to 8th month) at river terrace (flood-prone areas) along the coast of Akita (Omono river), Niigata (Agano river, Shinano river), and Yamagata (Mogami river). Prior to the advent of antibiotic therapy for the disease, it was a dreaded disease with 20% to 40% mortality rate. On the other hands, in 1948, American soldiers stationed in the foothills of Mt. Fuji (Shizuoka Pref.) contracted an unknown

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Correspondence:
Takaaki Yoshimoto, Department of Internal Medicine, Hitachi-Ota City Kegano Clinic, Ibaraki, Japan, E-mail: ymta@beige.ocn.ne.jp

Received Date: *01 Oct 2019*
Accepted Date: *25 Nov 2019*
Published Date: *02 Dec 2019*

Citation:
Yoshimoto Takaaki, Yoshimoto Taiji. Scrub Typhus in Japan. Am J Clin Microbiol Antimicrob. 2019; 2(3): 1042.

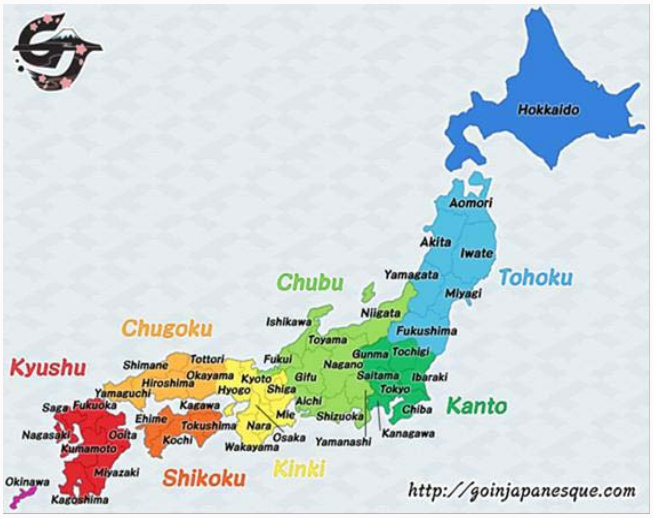

Image 1: (Map of Japan) Japan Honshu consists of five nominal regions and contains 34 prefectures, including metropolitan Tokyo.

fever, which was later proved to be scrub typhus transmitted by another type of *Leptotrombidium*. In contrast to the well known classical scrub typhus, febrile disease caused by *Leptotrombidium scutellare, Leptotrombidium pallidum* and other mites are classified as new type of scrub typhus. They include Shichitou fever (in Izu Shichitou islands), Hatsuka fever (20 days fever in Chiba), and Oppon of Tosa (in Kochi), Umayado disease (in Shikoku), a total of about 60 colloquial expressions, usually named after different endemic areas or duration of fever (e.g. Hatsuka means 20 days).

Scrub typhus in Taiwan (including Pescadores islands, Kinmen and lan-yu islands) during 1895 to 1945 under Imperial japanese occupation

Hatori Juro, a Japanese government preventive medical official in Taiwan, first described Tsutsugamushi fever in his paper "On the concordance of eruptive lymphadenitis fever in Formosa with Tsutsugamushi disease" in 1908 [5]. A total of 250 cases of scrub typhus were recorded from 1912 to 1914, with 23 deaths, 9.1% mortality rate, highest death rates in the aged and females, more cases in Japanese immigrants than in Taiwanese, and lowest morbility amongst aborigines. Cases were reported from Hualien, Chia-I, Ilan, Ochid island and Pescadores islands. The vector was confirmed to be *Trombiculum deliense.*

In the period 1950-1975: During the 1950s, about 100 cases in Japan Honshu were reported annually, but decreased rapidly to about 10 cases each year during 1965 to 1975, most cases were reported in summer. Scrub typhus of classical (*L. akamushi*) type almost became a forgotten disease in this country. During that era, tetracycline and chloramphenicol antibiotics, effective for scrub typhus were often prescribed for febrile diseases. It is quite possible that patients of scrub typhus were healed easily by those antibiotics without further examination.

In the period 1976-2019: Re-emergence of scrub typhus: Re-emergence of scrub typhus in 1980s, attributed to new serotypes of scrub typhus, transmitted by the mites, *L. scutellare* and *L. pallidum* are distributed throughout all parts of Japan except Hokkai-do. Up to 951 cases were reported in 1984. In recent 30 years, around 400 cases were reported each year. During the 1950 to 1970s, almost cases were reported during summer. However, after 1980, most cases were diagnosed in fall.

Chief Events of Scrub Typhus after 1998 in Japan

Expansion of endemic areas

A total of 29 cases of scrub typhus were reported in Okinawa. The first case was confirmed in 2008. Most patients were residents of Miyakojima island. Serotypes of scrub typhus were Taiwan Gilliam, Karp, mixed type of Gilliam and Karp. Most cases were diagnosed by nested-PCR and IFA.

First case of scrub typhus in urban area of Tokyo

A 33 years old man living in Ota district of Tokyo, contracted scrub typhus on November 4th, 2009. Skin eruption and eschar were not observed. Kawasaki serotype of ST was confirmed by nested PCR of blood.

Imported cases during recent 10 years

Among 4185 cases, 22 were imported cases. Seven patients were infected in South Korea, 3 cases in Cambodia, 2 cases in Malaysia, 1 case in Myanmar, while 5 cases remained unknown [6]. A 52 years old woman living in Yamagata contracted Boryong (almost 100% homology to Kuroki) serotype scrub typhus, during her stay in South Korea in early November 2015. A 49 year-old man was diagnosed as scrub typhus of Gilliam serotype after his return to Japan from Myanmar.

A case of classical type of Tsutsugamushi disease was confirmed in 2008 August in Akita

A 17 years old female contracted a Kato serotype of scrub typhus was diagnosed in 2008 August in Akita after an interval of 15 years.

Category IV Infectious Diseases in 1999

Scrub Typhus (ST) and Japanese Spotted Fever (JSF) are classified as 4th notifiable infectious disease designated by government ordinance in 1999. According to this law, physicians should immediately report laboratory confirmed cases of these rickettsial infection to the nearest healthy bureau.

Discussion

Although a disease caused by the bite of small red bug was described in China during 3rd century AD. Hakuju Hashimoto, a Japanese researcher, first described the disease in detail in 1810 in people living on the banks of Shinano River and called it "Tsutsugamushi". Tsutsuga means disease, while mushi means mite in Japanese. Scrub typhus has been prevailing in South-Asia (Tsutsugamushi Triangle). During 2nd world war, 18,000 cases were observed in Allied troops stationed in rural or jungle areas of the Pacific theatre. Nowadays, cases are no longer restricted to these areas. Patients of ST outside of the triangle were reported in Africa, France, Middle East, and South America after 2010 [8]. Scrub typhus could be simply classified as classical and new serotypes as shown in (Table 1). Most Japanese commercial laboratories usually measure the antibodies against three standards. In Kyushu, Yamagata and some other endemic areas (Kanto areas) 3 new serotypes should be checked.

During the recent 10 years, 4,185 cases were reported in Japan. Most cases (90%) are reported from Kyushu (Kagoshima, Miyazaki), Tohoku-Hokuriku, (Fukushima, Niigata, Akita, Yamagata), and Kanto areas (Kanagawa, Chiba). Scrub typhus has a large peak in autumn (10th to 12th month), and a small peak in summer (5th to 6th month). In northern Japan, most cases were diagnosed in the months of May through July and in October to December, whereas in southern

Table 1: Classical versus new type of scrub typhus.

	Classical	New	
Vector	*L. akamushi*	*L. scutellare*	*L pallidum*
Serotype	Kato	Kawasaki, kuroki	Gilliam, Karp
Virulence	Strong	Weak	Weak
Season	Summer (7th to 8th month)	autumn- winter and autumn	spring (4th to 6th month)
Distribution	Tohoku, Akita, Niigata, along river terrace prevalent before World War II	Yamagata Kyushu south Fukushima kanto areas, a large peak in autumn	Tohoku, Kagosima

Japan, cases were reported almost year round with a peak during October through December. As a result of population ageing in Japan, elderly people living in rural areas spending more time in outdoor activities (for instance, working in farm and forestry), are more likely to be exposed to infected mites. The peak incidence were in the age group of 60s to 70s, mean age of patients were 68 (male 66, female 71). Male constituted 54% of total cases. Expansion of endemic areas (first case in Okinawa in 2008), and urbanization of the infection pose a public health problem. This trend is also observed in Korea, China, and Thailand. A recurrent scrub typhus case after one year in an Okinawa patient (73 years-old female) suggests that the vector could carry several different genotypes of *Orientia tsutsugamushi*, (as many as six). Phylogenetic information revealed three strains, Gilliam Taiwan, Karp-variant and Saitama-variant; these serotypes were also reported in Taiwan [9].

Life cycle of a *Leptotrombidium* mite consists of egg, larva, nymph (protonymph, deutonymph, tritonymph), and adult. Transovarial and transstadial transmission are the main mechanisms for maintaining *O.tsutsugamushi* infection. Transstadial transmission is maintenance of the pathogen in the vector from one life stage to the next, passage of *O. tsutsugamushi,* from mite larva to nymph, and nymph to adult. Transovarial transmission is the process of passing *O. tsutsugamushi* from the female to offspring through eggs. Both the nymph and the adult are free-living in the soil. The six-legged, 0.2 mm chigger is the only stage that can transmit the disease to humans and other vertebrates. Chiggers do not pierce the host skin but rather take advantage of hair follicles or pores. The larvae will attach by inserting their chelicerae into the skin of the patient. Chiggers feed by extracting enzymatically liquefied tissue and epithelial cells via a feeding tube stylostoma that is formed by the incited immune reaction of the host to repeated infection of saliva into the wound. The saliva that the mites secrete can dissolve host tissue around the feeding site, and the mites ingest the liquefied tissue. The duration of attachment varies significantly between species. Usually the feeding lasts 2 to 4 days. Interestingly, the stylostoma formed by mite of *L. scutellare* is shallow (confirmed to epidermis), while that formed by *L. pallidum* and *L. akamushi* may penetrate to lower layer of skin (dermis).

The activity of larva is affected by diverse environmental changes, meteorological conditions, maximum and minimal air temperatures, relative humidity, and wind speed, duration of sunshine and cloud amount. The seasonal occurrence of scrub typhus varies according to climate in different countries and the disease is found to occur more commonly during rainy season [10].

The weather condition are very similar in Koriyama (Japan), Chounju (Korea), and Jinanin (China), three endemic areas of scrub typhus transmitted by *Leptotrombidium secutellare*, as shown in Table 2. Ground temperature around 10°C to 20°C is optimal for the activity of chigger of *L. scutellare,* therefore, Kawasaki and Kuroki serotypes of Tsutsugamushi contribute to the large peak of incidence

Figure 1: Skin eruption of scrub typhus in a 72 years old male patient, a typical case of scrub typhus (Kuroki serotype).

Figure 2: An Eschar in left axillary fossa of a 72 years old male patient. He did not notice the skin lesion.

in November. In contrast, *L. pallidum* (vector of Karp and Gilliam serotypes) distribute in To-Hoku and Hokuriku districts, active in autumn and spring (hibernation during winter under snow), is reflected by a small peak in May.

Fever (95% to 98%), skin eruption (86% to 93%), and eschar (85% to 88%) are three major clinical symptoms. Individuals of Japanese and Korean ancestries are more likely to develop a rash compared with Southeast Asians. Skin rashes usually develop on day 1st to 5th of illness. Eruption may be transient and easily missed. Actually, two possibilities exist in cases of ST without eruption, the first one, patients really do not exhibit skin rashes throughout the clinical course, the second one, patients receive effective antibiotics therapy within 4 days after onset of fever, may run a course without rashes. The degree of fever depends on serotypes of ST, stage of the disease, age and immune status of the patients. Virulence of Kawasaki and Kuroki serotype are weak in comparison to Kato. High fever (higher than 102.2°F) was rare in in our treated patients. Most cases had a low grade fever (99.3°F to 100.3°F). Skin rashes (Figure 1) and an eschar over left axillary fossa (Figure 2) show a typical case of Tsutsugamushi disease in a 72 years old male contracted Kuroki serotype of scrub typhus. The patient visited our clinic with a low grade fever, 99.3°F for about two days.

Figure 3: An eschar over right flank area of a 70 years old female contracted Kawasaki serotype of scrub typhus.

Laboratory data also strongly suggestive of scrub typhus infection as shown below; white blood cell (WBC) 4500/μL, platelet 13.7 × 10^4/μL, C-reaction protein 5 mg/dl, aspartate transaminase (AST) 99 μ/L, alanine transaminase (ALT) 83 μ/L, gammaglutamyl transpeptidase (γ-GTP) 80 μ/L, lactate dehydrogenase (LDH) 474 μ/L, creatinine (Cr) 0.57 mg/dl, other laboratory data were not remarkable. IFA IgG/IgM (Kato, Karp, Gilliam, Kuroki, Kawasaki and Shimokoshi, with a highest titer, 320/ 2560 of Kuroki serotype) were checked 14 days after onset of fever. Such a typical case of scrub typhus usually had a dramatic response to effective treatment. If fever did not abate 48 hours after minocycline antibiotics, diseases other than ST should be considered. The elevated C-reactive protein, low platelet count, and impaired liver function test (AST, ALT, γ-GTP) are typical clinical manifestations of scrub typhus, empiric effective antibiotics, usually minocycline, should be prescribed before IFA (IgG/IgM of six serotypes) antibody assay.

Eschar is painless and not pruritic (Figures 2 and 3) . In classical type of ST, patients may remember a pain during being stabbed by akamushi larva. The percentage of eschar also varies among areas of endemicity, and the researchers. The number of eschar may be more than one (Figure 4). A thorough skin check (especially in atypical case of ST), including head, ear canals, axillary fossa, umbilicus, genital area and anal area should be performed by physician and nurse. A thorough check of skin, including genital areas in females, increased the percentage of eschar from 82.6% to 100% of ST cases, was reported by a Japanese researcher Dr. Araigorou. Therefore do not forget to find an eschar (repeat and repeat by physicians and nurses) in patients with fever of unknown origin.

In contrast to considerable variation of percentage of three main symptoms among races, impaired liver function is a very common finding of scrub typhus in different endemic areas and races. High percentage of elevated liver enzymes were reported by Berman in Vietnam [11], Hu in Taiwan [12], Chanta in Thaland [13], and Ogawa in Japan. Usually in the early stage of the disease, fever may be the only symptom and the patients might be diagnosed as fever of unknown origin. If the patients are treated with effective antibiotics within the first week, dissemination of the bacteria via vasculitis and privasculitis into lung, heart, liver, spleen, kidney and central nervous system (any organ) could be prevented. Yet, a substantial number of scrub typhus was underdiagnosed and untreated properly.

Contributing factors to resurgence of scrub typhus in Japan since 1976 are complicated and interrelated, tetracycline and chloramphenicol, antibiotics effective for scrub typhus, were replaced by β-lactam in the treatment of febrile iseases since 1980s.

Table 2: Climate of three endemic areas of scrub typhus transmitted by *Leptotrombidium secutellare*.

Endemic area	October	November	December
Japan (Koriyama)	19°C to 12°C	14°C to 4°C	7.6 - Minus 0.4°C
Korea (Chounju)	22°C to 9°C	14°C to 6°C	8 - Minus 3°C
China (Jinan)	22°C to 12°C	14°C to 4°C	6 - Minus 3°C

Figure 4: Multiple eschars at right lower extremity in a 56 years old male patient contracted Kawasaki serotype scrub typhus.

Climate change (global warming), deforestation, road rebuilding, abandoned paddy fields, certainly affect the abundance and geographic distribution of disease vectors. We should acknowledge that there are new *Orientia* species and potentially new vectors for ST. Some vectors may disappear or expanding into new geographic areas, whereas others may disappear. Our study disclosed that Kuroki and Kawasaki were main serotypes of scrub typhus in Ibaraki area after 1998. While a survey conducted in 1984 revealed that the major serotype was Karp. The serological gene shift in this prefecture was in accordance with the deduction mentioned above.

During 2007 to 2016, most cases, 85% (3553) cases were diagnosed by Immunofluorescence Antibody (IFA) or Indirect Immunoperoxidase Test (IIP), 19% (806) cases by PCR of blood and/or eschar, 5% (217 cases) by isolation and 23 cases by pathology [6]. Weil-Felix test, by virtue of its long history and simplicity, has been one of the most widely employed tests for rickettsial infection on a global scale. The test is based on cross reactions between antibody produced in acute rickettsial infections with antigens of OX (OX19, OX2, and OXK) strains of Proteus. It has been superseded by more sensitive and specific tests in Japan.

In primary infection with *O. tsutsugamushi,* a significant high titer of IgM is observed during 10^{th} to 14^{th} day, whereas maximum IgG antibody appears about 3 weeks after onset of symptoms. IgM levels gradually declined but remain up to 6 to 12 months post-infection; IgG remained elevated above the diagnostic cutoff for 36 months. Our data revealed that significant level of IgG may last up to 25 years after infection.

Diseases which must be considered in the differential diagnosis include dengue fever, leptospirosis, infectious mononucleosis, typhoid fever, drug eruption, viral infection with eruption. Scrub typhus and Japanese spotted fever are two main rickettsial febrile infections in Japan. JSF occurs mainly in warm areas along the Pacific side of southwest and central Japan (Western Japan). Clinical findings more frequently observed in JSF than in ST patients were palmar and plantar rash, purpura, hypernatremia, organ damage, and delayed defervescence. Therefore, combined therapy of minocycline with fluoroquinolone was often prescribed. Moreover, the possibility of co-infection with another pathogen should also be considered if the patient's condition does not respond to treatment as expected. Co-

infection of scrub typhus with dengue fever [14], leptospirosis [15], Japanese spotted fever [16], Q fever [17], and acute hepatitis A were reported [18].

Nested Polymerase Chain Reaction (PCR) with patient's blood puffy coat and eschar before antibiotic therapy can be used for early diagnosis of scrub typhus before significant titer of antibody to O. *tsutsugamushi* develop.

Minocycline 200 mg/D for 7 days is the standard treatment for adult in Japan. Doxycycline resistant strains have been documented in parts of northern Thailand. Minocycline resistant cases of ST have not been reported in Japan. Azithromycine is the treatment of choice for pregnant woman and in young children under 8 years-old.

Conclusion

Scrub typhus is a potentially fatal but treatable disease. Health care providers in any countries must have a high index of suspicion for scrub typhus in febrile patient with a past history of exposure to infected mites in endemic regions. A diligent search for eschar is often rewarding. It clinches a diagnosis of scrub typhus and enables early initiation of treatment.

Competing Interest

The authors declare that they have no competing interest exist.

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