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MAJOR ARTICLE

Masqueraders Around Disaster: Clinical Features of Scrub Typhus in Fukushima, Japan

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Background. Scrub typhus (ST) is endemic in Fukushima, with the largest number of cases reported in Japan from 2009 to 2010. Although ST is highly treatable, its atypical clinical presentation impedes diagnosis, causing delays in treatment.

Methods. We review the clinical features of ST in adults from 2008 to 2017 at Ohta Nishinouchi General Hospital in Fukushima, Japan.

Results. Fifty-five cases (serotype Karp 24, Irie/Kawasaki 21, Hirano/Kuroki 10) of ST were confirmed via serology based on elevated immunoglobulin (Ig)M and IgG and polymerase chain reaction positivity of eschar samples. The mean age was 69 years, and 64% were female. The case fatality rate was 1.8% (1/55). Approximately 70% of cases (38/55) were not diagnosed as ST upon the initial clinic visit. Inappropriate use of antibiotics was identified in 22% of cases (12/55). In terms of atypical clinical features, 1 or more of the manifestations, fever, rash, and eschar, was absent in 31% of cases (17/55). Approximately 11% of cases presented without eschar (6/55; Karp 1, Irie/Kawasaki 1, Hirano/Kuroki 4). Moreover, severe complications were observed with shock and disseminated intravascular coagulation in 7% of cases (4/55), Thus, while 53% of cases presented with the typical triad (29/55), unusual complications and atypical features occurred in 40% (22/55).

Conclusions. Diagnosis of ST becomes clinically challenging in the absence of typical features. In Fukushima, an endemic area of ST, an atypical presentation involving multisystem disease is common.

Keywords. atypical clinical feature; Great East Japan Earthquake; *Leptotrombidium scutellare*; November fever; scrub typhus without eschar.

Scrub typhus (ST) is a neglected re-emerging infectious disease. One million cases of this multisystem disease occur annually worldwide, with an estimated 13% case fatality rate in the absence of appropriate treatment [1, 2]. ST is currently the most common rickettsiosis disease in Japan. From 2007 to 2021, 6576 cases were reported per year, compared with 300–500 cases per year in the late 1970s [3]. With few exceptions, 2 major forms of ST have been recognized: (I) a "spring-summer type" associated primarily with the vector *Leptotrombidium pallidum* (serotype Karp) in northeast Japan and (II) a "late autumn type" associated with the vector *L. scutellare* (serotype Irie/Kawasaki and Hirano/Kuroki) in west Japan [3, 4]. In addition, Asian strains of ST with the vector *L. deliense* have also been reported in the Ryukyu islands of Okinawa, Japan [5].

ST is an important endemic vector-borne disease in Fukushima prefecture, with the highest reported cases in 2009–2010 [3]. The first patient with ST in Fukushima prefecture was reported in May 1972 in Tenei village [6]. Subsequently, ST has become endemic in Fukushima over the last 50 years as a re-emerging infectious disease.

The Great East Japan Earthquake (GEJE) in 2011 and the subsequent accident at the Fukushima First Nuclear Power Plant had considerable environmental impacts, affecting not only humans but also wild fauna and flora [7]. Historically, ST around endemic river sites was called "Japanese flood fever" [8]. Despite this, the relationship between the epidemiological characteristics of ST and the environmental changes caused by natural disasters has been neglected by experts. Consequently, the impact of the GEJE on endemic diseases in Fukushima, including ST, remains unclear.

This study evaluates the diversity of the clinical features of ST, typically overlooked upon atypical presentation, to improve

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the differential diagnosis of this disease and facilitate timely and appropriate treatment.

METHODS

This study was conducted at Ohta Nishinouchi General Hospital, a tertiary referral center with 1086 beds in Fukushima prefecture, Japan. This medical center services the central area of the Nakadori region and the surrounding countryside of Fukushima prefecture. This region is an endemic area of ST. Located on the 37th parallel north, it has the same latitude as southern Shandong province in China [9] and southeastern Korea, other known endemic ST areas [10].

Study Design and Setting

We retrospectively reviewed 55 diagnosed cases of ST at Ohta Nishinouchi Hospital from 2008 to 2017 (inclusive), from which a standardized database was constructed including patient clinical information, vital signs, physical findings, eschar sites, eschar recognition, outdoor activities, laboratory data, complications, comorbidities (Charlson comorbidity index), treatment options, prognoses, and diagnosis before or after the GEJE in 2011. All data were obtained from electronic and paper medical records. We defined "ST without eschar" as ST with no indication of eschar upon physical examination. The follow-up period was conducted until December 31, 2017 (inclusive). Disseminated intravascular coagulation (DIC) was defined clinically as the activation of coagulation pathways, resulting in the formation of intravascular thrombi and depletion of platelets and coagulation factors, complicated by multi-organ failure accompanied by specific laboratory data including prolonged partial thromboplastin time (PTT), hypofibrinogenemia, and thrombocytopenia.

Laboratory Methods

A confirmed laboratory diagnosis of ST was defined as a >4-fold increase in the immunoglobulin (Ig)M or paired IgG titer of the indirect immunoperoxidase assay (Ohara Research Laboratory, Fukushima, Japan, and Mahara Institute of Medical Acarology, Anan, Japan) [4] or when a positive result was obtained for the nested polymerase chain reaction (PCR) of the 56-kDa type-specific antigen gene of *Orientia tsutsugamushi* (Miyazaki Prefectural Institute for Public Health and Environment, Miyazaki, Japan and Fukushima Prefectural Institute of Public Health and Environment, Fukushima, Japan) [11] from the clinical specimens, including eschar, whole blood (drawing complete blood count test tube), and others (synovial/cerebrospinal fluid). Six serotypes of *Orientia tsutsugamushi* (OT) have been identified: Kato, Karp, Gilliam, Irie/Kawasaki, Hirano/Kuroki, and Shimokoshi [12]. Obtained serum samples were diluted from 1:40 to 1:40 960 for the immunoperoxidase assays. The titer of each sample was expressed as the reciprocal of the highest dilution.

Statistical Analysis

The clinical characteristics of the ST cases were summarized and compared according to 2 categories: before and after the GEJE. Chi-square and Fisher exact tests were used to compare categorized variables, and the Student *t* test was used to compare continuous variables in the database analysis in STATA (version 15.0; StataCorp LCC, College Station, TX, USA).

RESULTS

A total of 55 ST cases were diagnosed. The mean age (range) was 69 (37–90) years, and 64% of the patients were female. Regarding laboratory diagnosis, 31 cases (31/55, 56%) were positive for serological and PCR testing. Twenty-three cases (23/55, 41%) were only positive for serological testing. The singular fatal case was diagnosed by PCR only [13]. Therefore, a total of 32 cases were diagnosed by PCR, followed by sequencing of type-specific antigens for the 56-kDa gene (432 bp) (Figure 1). The serologically diagnosed types of ST included Karp (24 cases, 43%), Irie/Kawasaki (21 cases, 38%), and Hirano/Kuroki (10 cases, 18%); neither the Gilliam nor Shimokoshi type was observed in our cohort. These results were corroborated via phylogenetic tree analysis, with ST diagnosis based on serotypes and genotypes made for 32 cases, excluding the 1 case that was not serotyped due to patient death. The cases of serotype Karp were identified via sequencing as the Karp JP-1 and JP-2 phylogenetic types after PCR [14]. Similarly, the cases of Irie/Kawasaki and Hirano/Kuroki serotypes were genetically identified as Kawasaki and Kuroki, respectively (Figure 1).

Site of Infection Contraction

The locations where patients may have been bitten by a larval-stage (chigger) trombiculid mite carrying OT, denoted "mite island" [15], were estimated. The resulting sites were plotted on a web mapping platform (Google Earth), along with their identified serotypes/genotypes. However, this was not possible for the fatal case. Additionally, 2 of the cases (sisters) were bitten at the same location and were thus treated as 1 ST location in the plotted areas. The resulting estimated site of infection (ie, "mite island") was at latitude 36°55′ to 37°40′N and longitude 140° to 140°45′E (Figure 2). Each of the ST serotypes was distributed as follows: (i) Karp: mountainous area; (ii) Irie/Kawasaki: urban district; (iii) Hirano/Kuroki: suburb.

The seasonal distribution revealed that infection with Karp—the "spring-summer type" associated primarily with the vector *L. pallidum*—peaked between April and May (18/24, 75%). By contrast, infection with Irie/Kawasaki and Hirano/Kuroki—the "late autumn types" associated with the vector *L. scutellare*—peaked in October to November (21/21, 100%, and 10/10, 100%, respectively). Two cases of Karp serotype infection occurred in December and January. The patient

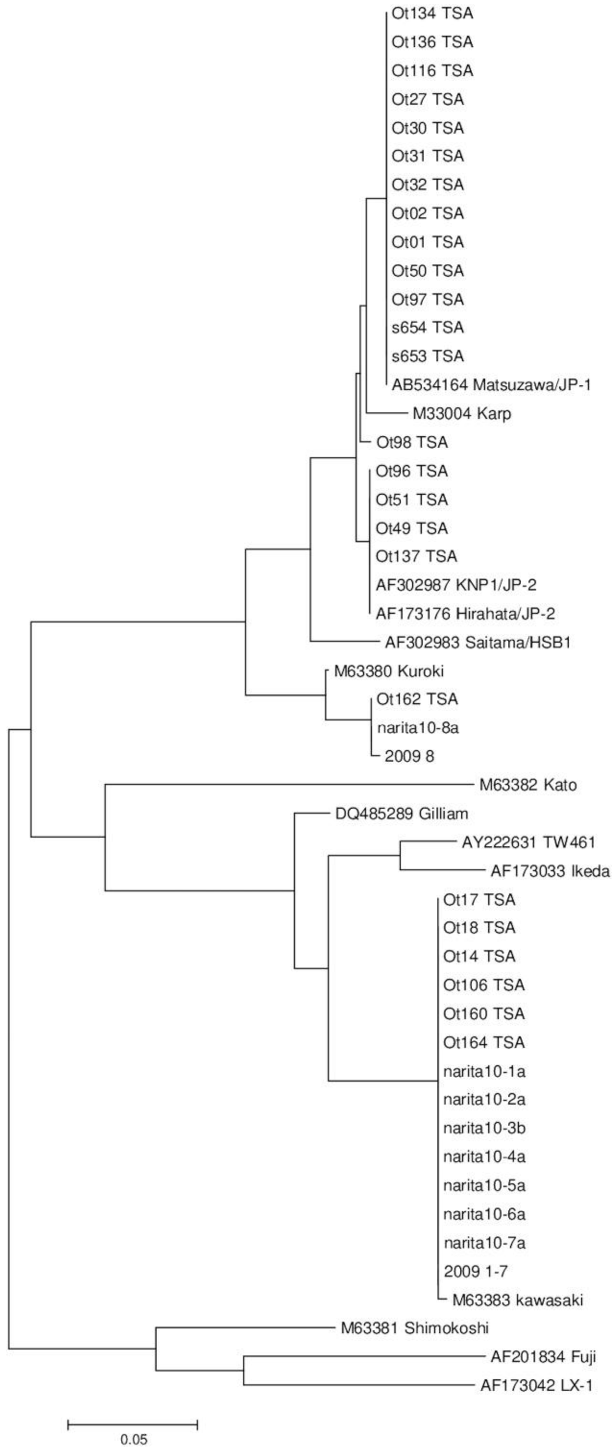

Figure 1. Phylogenetic tree constructed using the sequences of type-specific antigens for the 56-kDa gene (432 bp): Descriptions on stains are samples for sequencing using eschars, whole blood, and synovial fluid, named by researchers in order of the reception of specimens.

delay (PD; days from onset to initial visit), hospital delay (HD; days from initial visit to treatment), and treatment delay (TD; PD + HD) (range) were 3.4 (0–11) days, 3.3 (0–17) days, and 6.8 (0–23) days, respectively. The average number of visits to the hospital before diagnosis (range) was 2 (1–6). Regarding patients' activities, 96% (53/55, 2 cases unknown) undertook gardening or walking. Episodes of outdoor excretion (urination with or without defecation) were observed in 11% of the ST cases (6/55; all women, 3 cases unknown). Two sisters infected at the same location both urinated outside during rice transplanting and were infected with the same serotype and genotype (Karp JP-1 ST). Eschar recognition by the patients was observed in 20% of the cases (11/55). Lastly, 2 cases of altered mental status due to ST infection were noted while taking a hot spring bath, including the fatal case [13].

Regarding the key clinical features of ST among the 55 cases, fever (≥38.0°C), rash, and eschar were observed in 81%, 91%, and 89% of cases, respectively. Other features included general fatigue (71%), anorexia (75%), headache (36%), lymphadenopathy (49%), elevated lactate dehydrogenase (>250 U/L, 100%), elevated fibrin degradation products (≥4 μg/mL, 75%), elevated D-D dimer (≥1.0 μg/mL, 76%), and atypical lymphocytosis (95%).

Among the hospitalized patients with ST, the mean number of hospital-days was 13.6. The antimicrobial agents administered as part of the treatment were minocycline (parenterally and orally; 62%, 34/55) and doxycycline (orally; 35%, 19/55). The mean treatment duration was 11.1 days. No combination therapy with intravenous tetracyclines or azithromycin was administered. Notably, in 2 cases, the infection resolved without treatment. Inappropriate use of antimicrobial agents for ST was observed in 22% of the cases (12/55). The case fatality rate was 1.8% (1/55): 1 fatal case with the Kuroki serotype was diagnosed by PCR from eschar [13]; all other cases survived the clinical course of ST.

Categorized Clinical Features of Scrub Typhus

A total of 55 ST cases were categorized according to 4 clinical features based on 2 characteristics: severity (severe, moderate, or mild) and diversity (typical, moderate, or atypical) (Figure 3): (i) Category 1 (29/55, 53%; fever ≥38.0°C, rash, and eschar) had no major organ involvement; (ii) Category 2 (4/55, 7%) had unstable vital signs, DIC, and/or bleeding and required intensive care; (iii) Category 3 (5/55, 9%) exhibited organ involvement with related symptoms and signs; (iv) Category 4 (17/55, 31%) lacked the major clinical triad (ie, fever, rash, and eschar) of ST.

Category 2 included 2 cases of Karp JP-1 characterized by acute gastric bleeding [16] and Karp-related strain [14] with DIC complicated by hypovolemic shock. The 1 fatal case was caused by infection with the serotype Kuroki [13]. Category 3 included 4 cases of Karp, preceded by paroxysmal atrial fibrillation, syncope, pleural effusion, and ascites, respectively, and 1 case of Irie/Kawasaki complicated by encephalitis and aseptic meningitis (CSF PCR negative), left knee arthritis (synovial fluid PCR positive), acute gastroduodenal ulcer, atrial fibrillation,

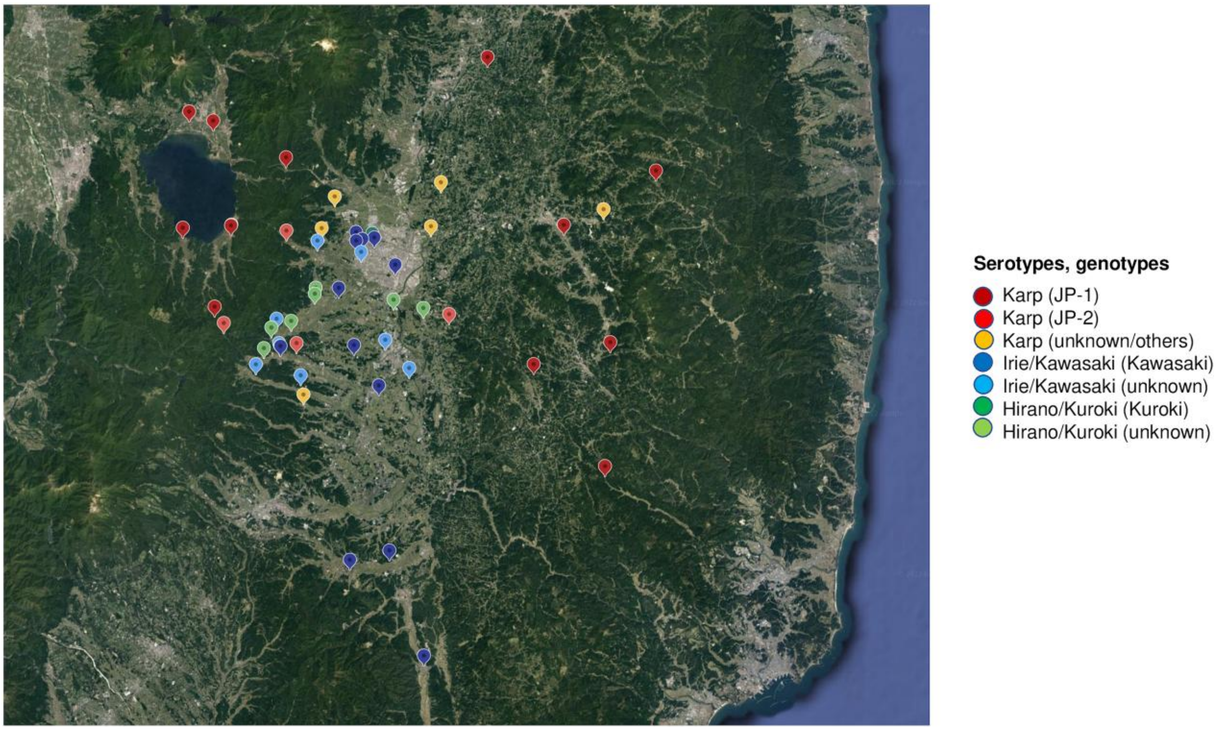

Figure 2. Estimated location of the "mite islands" for each serotype/genotype of scrub typhus in Fukushima, 2008–2017.

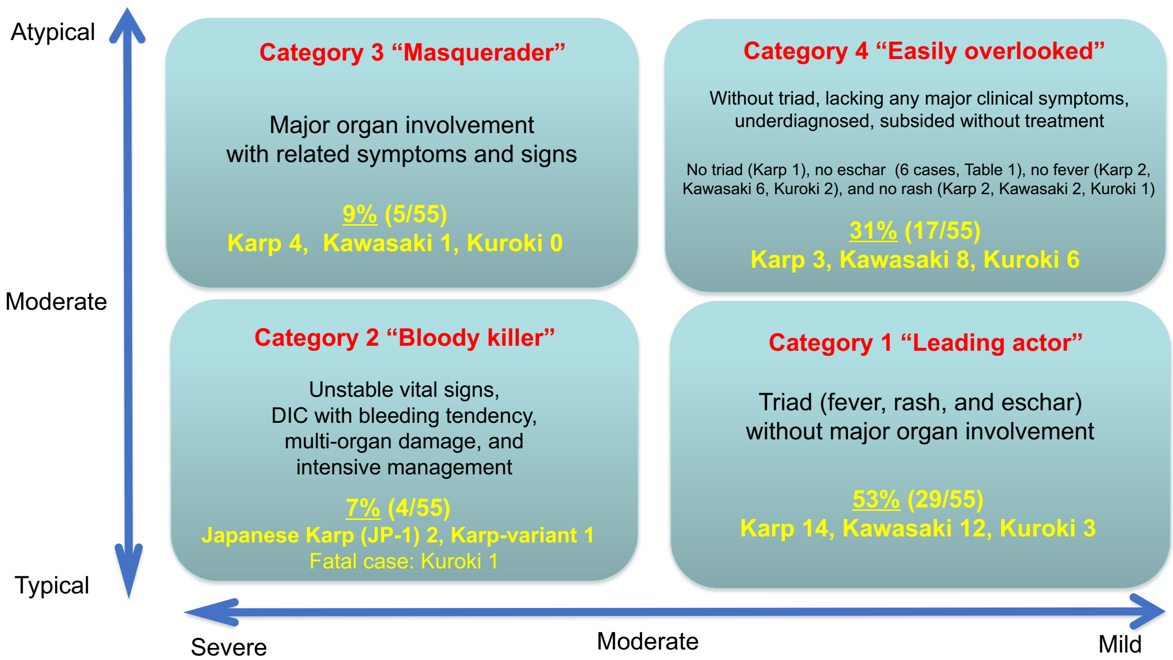

Figure 3. Categories of disease spectrum for scrub typhus in Fukushima, 2008–2017. Abbreviation: DIC, disseminated intravascular coagulation.

and acute renal failure. Category 4 included 1 case (serotype Karp) without any characteristic features of ST (fever ≥38.0°C, rash, and eschar), 6 who presented without eschar (11%) (Supplementary Table 1), 10 who were afebrile (Karp 2, Irie/Kawasaki 6, Hirano/Kuroki 2), and 5 who presented without rash (Karp2, Irie/Kawasaki 2, Hirano/Kuriki 1). For the 6 cases without eschar, the mean age of the patients (range) was 66.8 (52–85) years, and there were 3 male and 3 female. No

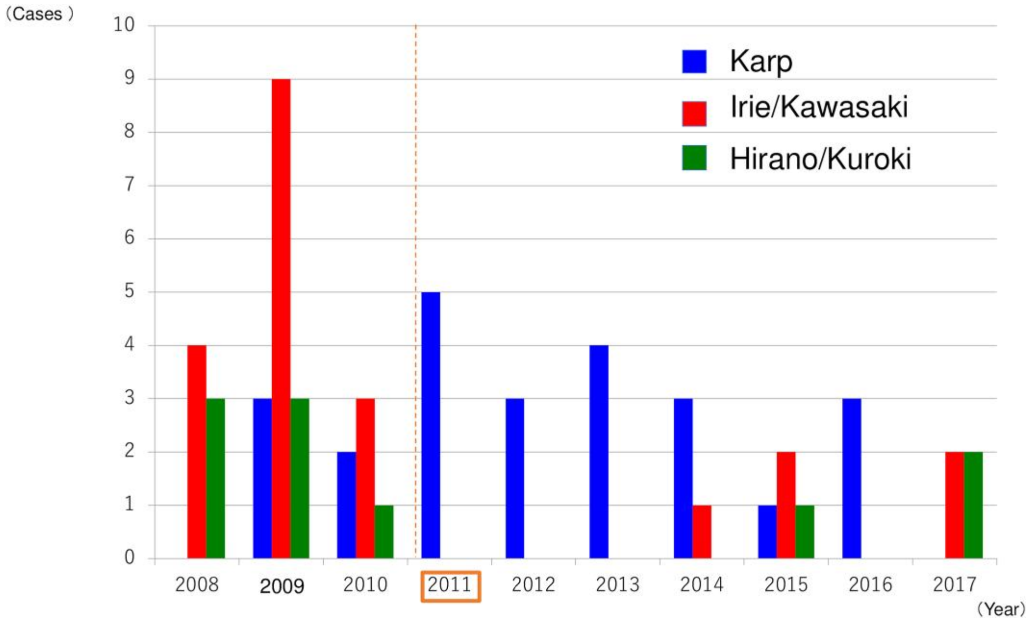

Figure 4. Trend of each scrub typhus serotype in Fukushima, 2008–2017.

treatment was needed in 2 cases. Although no fatalities were recorded, 2 of the cases died of underlying diseases during the follow-up period. All 6 cases of ST without eschar had comorbidities. However, the relationship between eschar and comorbidities was not significant ($P = .978$). Systemic signs and symptoms, laboratory abnormalities, presumptive/differential diagnoses, and complications were observed in all 55 cases of ST (Supplementary Table 2). Sixty-nine percent (38/55) of the ST cases were not identified as such upon differential diagnosis at the initial visit.

Regarding the differences in clinical features before and after the GEJE, the Karp, Irie/Kawasaki, and Hirano/Kuroki serotypes exhibited significant differences ($P = .000$; Supplementary Table 3). No cases of Irie/Kawasaki or Hirano/Kuroki were observed, and no changes in Karp were detected from 2011 to 2013 (Figure 4). Additionally, a declining trend in the prefectural reported number of ST cases in Japan from 2007 to 2021 was observed in Fukushima prefecture after 2011 [3]. This is in stark contrast to the 3 prefectures with the highest rates of infection (Kagoshima, Miyazaki, and Chiba), which have exhibited increases, albeit with fluctuations (Figure 5).

DISCUSSION

This study provides an overview of the diversity of the clinical features of ST, from typical to atypical presentation, with multisystem complications, and highlights its nature as a spectrum of disease. We have categorized the clinical features (Categories 1 to 4) along the clinical spectrum of ST (Figure 3). Atypical presentation, in particular without the triad of symptoms (fever, rash, and eschar), makes it particularly difficult to diagnose in primary health care settings. Furthermore, the absence of the diagnostic key, namely eschar, poses challenges. An eschar is the entry site for chigger bite inoculation of OT, where a high concentration of the organism resides. As such, they provide meaningful diagnostic information despite the positive rate of recognition (7%–97%). As reported previously, accurately diagnosing ST in a formal clinical setting depends on the background of the patient, including ethnicity, age, and sex [9, 17–24]. Moreover, the absence of an eschar may be influenced by the virulence of the ST strains, the amount of inoculated OT, underlying diseases, and the immune status of patients.

The differences in the virulence of different ST serotypes, phenotypes, and genotypes are currently unknown. In terms of clinical features, ST virulence varies depending on the OT strain and the background or comorbidities of the patient. Indeed, the current study results aptly revealed variable virulence among the strains, from a fatal case of ST with the relatively low virulence Hirano/Kuroki serotype [13, 25] to a nonfatal clinical presentation of the Karp serotype that resolved without treatment (Type 4) (Figure 3; Supplementary Table 1).

The observed decline in ST cases after 2011 between the *L. scutellare*–mediated serotypes (ie, “late autumn type,” also known as November fever [13, 26]) and the total number of reported ST cases in Fukushima prefecture is interesting. However, accurately defining the associated relationship between these phenomena, the GEJE, and a subsequent nuclear power plant accident is difficult. Indeed, any number of issues related to the environment, vector, patient, and health care system could be contributing factors to the decline in ST cases.

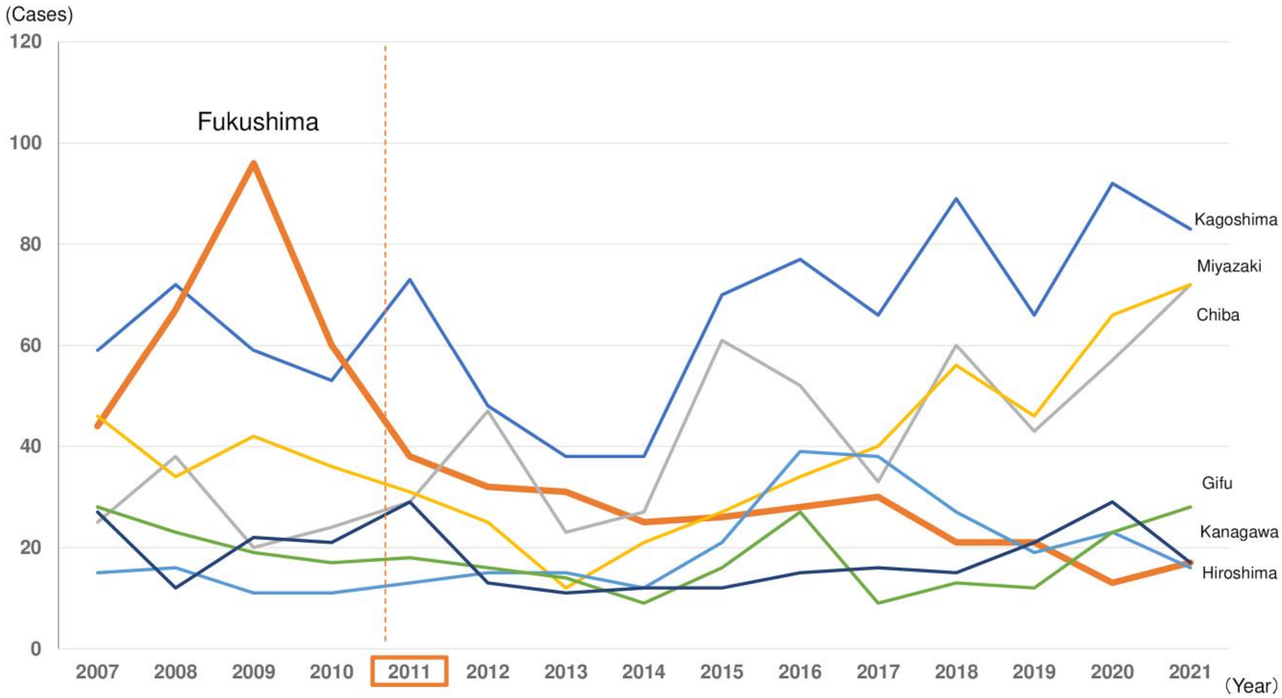

Figure 5. Frequency of reported scrub typhus cases in Japan, 2007–2021.

The GEJE caused damage to superficial soil in the endemic region of ST in Fukushima, Japan, including during the decontamination operation after the first Fukushima nuclear power plant accident. In addition to the damage caused by the tsunami following the GEJE to coastal areas of the Hamadori region, the inland central area of the Nakadori region was also damaged, leading to the complete failure of an embankment (earth-hill) dam and uncontrolled discharge being released throughout the valley, destroying riverside villages and killing 8 people [27]. Notably, the damaged basin of this dam was located in the endemic region of the subtypes transmitted by *L. scutellare*, that is, Irie/Kawasaki and Hirano/Kuroiki ("late autumn type" ST) [3].

The 2 major vectors of ST in Fukushima are *L. pallidum* and *L. scutellare,* which transmit the Karp and Irie/Kawasaki and Hirano/Kuroki serotypes, respectively. With regards to zoology and arthropodology, *L. pallidum* has an affinity for *Microtus montebelli* (Japanese grass vole) and *Eothenomys andersoni* (Japanese red-backed vole). Conversely, *L. scuttelare* has very low host specificity for small mammal hosts (eg, rodents and mice) and other mammals (eg, deer and wild boars), birds, and reptiles, as well as humans [28]. Although the effect of the GEJE on the bacterial hosts and their environment is immeasurable and multifactorial, *L. scuttelare* seems to be more susceptible to the effects of environmental changes than other vectors in terms of nonspecific preference. That is, *L. scuttelare* may be more vulnerable to large-scale environmental change.

After the GEJE, the failure of the established social systems to react in a timely and comprehensive manner had negative effects on physical, psycho-social, and behavioral outcomes, noting, for example, increased frailty among elderly patients [29]. This may partially account for the decrease in the number of reported ST cases in Fukushima. The health care system in the regions closest to the Fukushima First Nuclear Power Plant collapsed after the GEJE [30]. This included the adjunctive area, an ST-endemic area in Fukushima prefecture [31]. Although ST diagnosis remains a challenge globally [32], as evidenced by the delay in diagnoses from the time of onset of almost 1 week reported in this study, no fatalities were reported due to health care system failures in response to the GEJE.

In terms of the relatively high mortality of ST, not least from a global standpoint, the effectiveness of antimicrobial treatment for severe ST is a pressing issue. Combination therapy with intravenous doxycycline and azithromycin in cases of severe ST is associated with a lower incidence of composite primary outcomes (ie, cardiovascular, respiratory, central nervous system, renal, and hepatic system complications) than a single administration of doxycycline or azithromycin. Meanwhile, similar rates of 28-day mortality are achieved following treatment with doxycycline or azithromycin alone or in combination [33]. However, caution must be taken when extrapolating these results to other ST-endemic areas. The 28-day mortality rate (ie, death at day 28) in the study by Varghese et al. [33] was 12% (96/794), higher than that in our study cohort (1.8%, 1/55) and that of another study in Japan (0.5%, 1/188) [34]. The difference in mortality rates among these ST-endemic areas reflects strain virulence, including differences between *L. delicense*–mediated strains in India and *L. scutellae*–mediated strains (serotype Irie/Kawasaki and Hirano/Kuroki) in Japan. Additionally, the delay in treatment and accessibility to health care may represent other confounding factors. Importantly, the administration of combinatorial therapy with azithromycin could be associated with cardiovascular side effects, including cardiovascular death [35], which must be considered when selecting optimal treatment strategies. Moreover, the cost-effectiveness of combination therapy with intravenous doxycycline and azithromycin for treating severe ST warrants further evaluation.

This study has certain limitations. First, the study was performed at a single type of medical center, namely affiliated hospitals and clinics, in Fukushima, Japan. Based on the epidemiological background of ST, our results may not readily extrapolate to other areas, particularly in terms of the variations in ST serotypes and vectors, as well as interactions between vectors and animal hosts. Second, the diagnostic methods used between cases were not uniform: Either serological diagnosis or PCR, if not both, was performed. Clinical diagnosis based on history, especially epidemiological background and physical examination, followed by confirmed laboratory diagnosis, were applied. In addition, complete physical examinations of the genitalia, ear canals, and naval cavity were not performed, excluding those cases listed in Supplementary Table 1. The patients in the clinical cohort were thought to represent potential cases of ST infection; however, other cases with unusual clinical presentation (ie, Category 4 in Figure 3) might have been missed, even with a high index of suspicion. Third, unclassifiable cases of ST may occur when attempting to classify cases into 1 of the 4 categories (Categories 1–4). The 2 axes (ie, severity and diversity) used in this study for diagnosis are continuous as a clinical spectrum per se. As the purpose of this study was to describe the variety within the clinical features of ST, the use of these categories simplified the characterization of the variable clinical features of ST. The masquerading of ST under other clinical conditions (Category 3) or an unusual clinical presentation lacking typical features, in particular for eschar (Category 4), is highlighted in this study. However, it is evident that there are variable clinical features of ST not included in the 4 categories.

In summary, ST is a multifaced, vector-borne, endemic, reemerging infectious disease that presents atypically (ie, without typical clinical features) and often masquerades as other diseases, which is why it can often go undiagnosed. As such, a high level of suspicion is needed when diagnosing this disease to prevent treatment delay.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Acknowledgments

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Author contributions. All authors contributed to the study conception and design. Data collection and analysis were performed by Masashi Narita. The first draft of the manuscript was written by Masashi Narita, and all authors commented on versions of the manuscript. All authors read and approved the final manuscript.

Patient consent. This study was approved by Institutional Review Board of Ohta Nishinouchi General Hospital (approval no. 2023-06).

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