American Journal of Medical Case Reports, 2015, Vol. 3, No. 1, 20-22
Available online at http://pubs.sciepub.com/ajmcr/3/1/8

DOI:10.12691/ajmcr-3-1-8

Atypical Case of Scrub Typhus

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Received December 25, 2014; Revised January 10, 2015; Accepted January 14, 2015

Abstract Scrub typhus, also called tsutsugamushi disease in Japan, is one of the most common rickettsial diseases in this country. Fever, skin rash, eschar and elevated hepatic enzymes are main clinical features of scrub typhus. We present the case of a 55 year-old woman contracted with this infection without skin eruption and abnormal liver function. The finding of an unusual eschar helped us to make a correct diagnosis. The fever subsided within 24 hours after minocyline therapy. Scrub typhus of Kuroki serotype was confirmed by indirect immunoperoxidase assay and nested polymerase chain reaction with her whole blood and eschar.

Keywords: *rickettsia, scrub typhus , eschar, skin eruption*

Cite This Article: Takaaki Yoshimoto, and Taiji Yoshimoto, "Atypical Case of Scrub Typhus." *American Journal of Medical Case Reports*, vol. 3, no. 1 (2015): 20-22. doi: 10.12691/ajmcr-3-1-8.

1. Introduction

*Orientia tsutsugamush*i, the causative organism of scrub typhus, is an obligate intracellular gram-negative bacteria. In contrast to other ri-ckettsia, it has a different cell wall structure and genetic composition, possesses neither lipo-polysaccharide nor glycoprotein in cell wall [1]. Humans are infected by chigger (the larva of mite*)* harbouring *O. tsutsugamushi.* The bacteria attack endothelial cells of small vessels, which may disseminate into lung, heart, pancreas, liver, spleen, kidney and central nervous system [2].

In Japan, there are 6 main serotypes of scrub typhus, 3 prototypes (Kato, Karp, Gilliam), Kawasaki, Kuroki, and Shimokoshi. They can be simply classified as akamushi (classical) and non- akamushi (new) types. The akamushi type, transmitted by *Leptotrobidium akamushi*, had been endemic before second World War since early 1800s. It occurred mainly in summer at river terrace along the coast of the sea of Japan, in the northeastern area of Akita, Niigata and Yamagata. In the pre-antibiotic era, it was a dreaded disease with 30% mortality rate. During the 1950s, about 100 cases were re-ported annually, but decreased rapidly to about 10 cases each year during 1965-1975. Scrub typhus of the classical type almost became a forgotten disease in Japan [3].

Re-emergence of scrub typhus in 1980s, attributed to non-akamushi (new types) scrub typhus, transmitted by the mites, *Leptotrobidium scutellare* (vector of serotypes Kawasaki and Kuroki) and *Leptotrobidium pallidum* (vector of serotypes Karp and Gilliam) are distributed throughout all parts of Japan except Hokkai-do. Up to 951 cases was reported in 1984. In recent 15 years, about 400 cases were reported annually [4].

2. Case Presentation

A 55 years old woman presented with a fever of 4 days. She had a past medical history of type 2 diabetes mellitus and had been on insulin injection for about 10 years. Physical examination showed that her blood pressure (BP), 120/70mmHg, a body temperature (BT), 38.1°C (axillary). A big ulcer over her left lower chest was detected. Yet, she had no skin rash (Figure 1). Blood routine revealed a white blood count (WBC), 7600 /μl, C-reactive protein (CRP), 5.8mg/dL, a blood sugar (BS), 270 mg/dL, and a weak positive urine ketone body. Aspartate aminotransferase (AST), alanine aminotransferase (ALT) and lactic dehydrogenase (LDH) were normal (15U/L, 10U/L and 220 U/L, respectively).

Figure 1. A big ulcer over left lower chest of a 55 year - old woman contracted with scrub typhus without skin rash and hepatic dysfunction

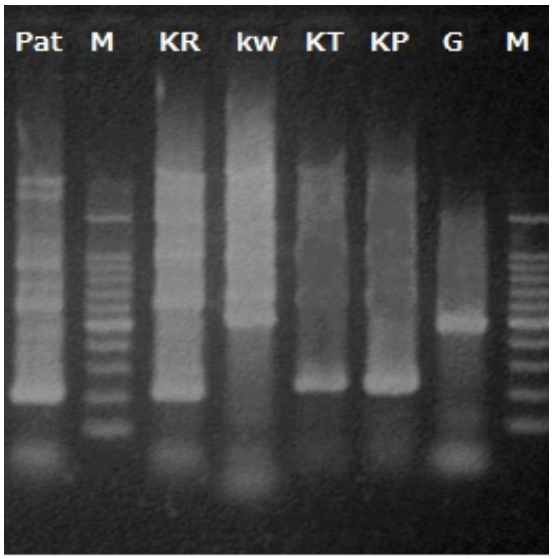
She had a dramatic clinical improvement to empirical oral minocycline 200mg/day, her fever abated wihin 24 hours after initiation of the antibiotics.

Indirect immunoperoxidase test (IIP) performed 10 days after onset of fever revealed a highest titer of antibody to Kuroki serotype of scrub typhus (Table 1). Nested polymerase chain reaction (PCR) with her whole

blood and eschar before minocycline therapy were conducted according to Furuya`s method [5]. Primers 34 (5`-TCAAGCTTATTGCTAGTGCAATGTCTGC-3`) and 55(5`-AGGGATCCCTGCTGCTGTGCTTGC TGCG-3`) were used for the first PCR, primers 10 (5`-GATCAAGCTTCCTCAGCCTACTATAATGCC-3`) and 11(5`-CTAGGGATCCCGACAGATGCACTATTAGGC-3`) for the second PCR. Gillam-specific primers 10 and G (5`CTTTATATCACTATATATCTT-3`), Karp-spe-cific primers 10 and KP (5`-ACAATATCGGATTTATAACC-3`), Kato-specific primers 10 and KT (5`-GAATATTTAATAGCACTGGA-3`), Kawasaki –spe-cific primers KW(5`-ATGCTGCTATTGATACAGGC-3`) and 11, Kuroki-specific primers 10 and KR (5`CACCGGATTTACCATCATAT-3`) were used for serotype-specific DNA amplications. The PCR products were analyzed by electrophoresis in a1.5-2% agarose gel containing ethidiumbromide and visualized under UV light. DNA from reference strains were used as positive controls (Figure 2). Indirect immunoperoxidase test and eschar PCR confirmed that she had a recent *O. tsutsugamushi* infection of Kuroki serotype.

Table 1. Antibodies against *Orientia tsutsugamushi* by indirect immunoperoxidase test (IIP). Numerals represent reciprocal of highest serum titer of antibodies

Serotype	Immunoglobulin (IgG)	Immunoglobulin (IgM)
karp	40	640
Gilliam	0	40
Kato	40	1280
Kawasaki	0	40
Kuroki	160	2560
Shimokoshi	0	0



Pat: patient KR: Kuroki KW: Kawasaki KT: Kato
KP: Karp G: Gilliam M: Maker

Figure 2. Agarose gel electrophoresis of amplified DNA by nested PCR with serotype-specific primers. A 220bp band specific for Kuroki serotype was detected

3. Discussion

Contributing factors to resurgence of scrub typhus in Japan since 1976 are complicated and interrelated. First, tetracycline and chloram-phenical, antibiotics effective for scrub typhus, were replaced by betalactam antibiotics in the treatment of febrile diseases since 1980s [6]. Second, dichlorodiphenyltrichloroethane (DDT) and benzenehexachloride (BHC), were no more used in Japan. Third, global warming, deforestation, road rebuilding, and abandoned paddy fields, might cause change in the epidemiology of the disease, some vectors may disappear, while others may introduce into new areas.

The mite has a four-stage life cycle: egg, larva, nymph and adult. The larva (chigger) is the only stage that can transmit the disease to humans and other vertebrates. The activity of chigger is determined by temperature and humidity. Ground temperature between 10-20°C is optimal for the activity of chigger of *L. scutellare*, which. only feed on human in autumn. Therefore, Kawasaki and Kuroki serotypes, prevalent in Kyushu (Kagoshima, Miyazaki), south Fukushima and Kanto areas, contribute to the large peak of incidence in November. On the other hands, *l. pallidum* (vector of Karp and Gilliam serotypes), distribute in To-hoku and hokuriku districts, active in both autumn and spring (hibernation during winter under snow), is reflected by a small peak in May [7].

The percentage of skin rash and eschar in scrub typhus varies among races and various studies. Individuals of Japanese and Korean ancestries are more likely to develop a rash compared with southeast Asians, who contract the disease. The percentage of eruption reported in Japan, Korea, southeast Asia are 93%, 90.7% and 20 % respectively [8].

Eschar, the location where the chigger feeds, pathogomonic of scrub typhus, can occur on any part of the body, such as scalp, axillary fossa, ears, breast, umbilicus, genitoanal region. The number of eschar may be more than one. The percentage of eschar reported in Japan and Korea were 87%, 78.9-94% respectively, but is seen less frequently in southeast countries. In some patients, a typical eschar may not form and the lesion may appear only as a denuded papule or ulcer. Usually, the patients are not aware of the eschar as it is painless and not pruritic. Therefore, a thorough skin check is imperative to find an eschar, which was often missed.

Berman reported that elevation of hepatic enzymes is frequently observed in patients with scrub typhus in Vietnam [9]. Hu reported liver function impairment in 29 of 30 scrub typhus patients in Taiwan [10]. In Thailand, 96.3% of 54 children diagnosed with scrub typhus had elevated liver enzymes [11]. Hepatic dysfunction in japanese patients were 91% reported by Ogawa[4]. In contrast to considerable variation of percentage of skin rash and eschar in races, hepatic dysfunction is a very common finding of scrub typhus in different endemic areas and races.

Indirect immunofluorescent antibody (IFA) and indirect immunopeoxidase test (IIP) are current gold standards for diagnosis of scrub typhus. However, these tests are retrospective, because significant antibody titer to *O. Tsutsugamushi* do not develop until 7-10 days after onset of fever. In Kyushu (Kagoshima, Miyazaki), Yama-gata and some other areas, 3 new serotypes, Kawasaki, Kuroki, and Shimokoshi should be added to 3 standards, Koto, Gilliam and Karp, for a correct serological diagnosis.

Nested polymerase chain reaction (PCR) with patient`s blood puffy coat and eschar before antibiotics therapy can

be used for confirmation of the infection in acute early stage of disease, especially in cases without rashes, in patients with atypical eschar [12] and sero-negative scrub typhus [13].

4. Conclusion

Physicians must have a high index of suspicion for scrub typhus in febrile patient with a past history of exposure to infected mites in endemic region.

Acknowledgement

The authors thank Dr. Hiromi Fujita, Chief of Ohara Research Laboratory for examination of serum antibo-dies.

Cover Letter

This manuscript (Atypical Case of Scrub Typhus) has not and will not be submitted for publication elsewhere so long as it is under consideration by the *American Journal of Medical Case Reports*. The article is original and has not already been published.

Competing Interest

The authors declare that they have no competing interests exist.

Funding

The authors have no support or funding to report.

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