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SCRUB TYPHUS AS MISSED DIAGNOSIS FOR ACUTE FEBRILE ILLNESS IN MALAYSIA, SOUTHEAST ASIA

By

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Abstract

Scrub typhus (Tsutsugamushi fever) is caused by *Orientia tsutsugamushi* (previous *Rickettsia*) and is transmitted to man by a mite vector of the *Trombiculidae* family (*Leptotrombidium deliense* and *L. akamushi*). Scrub typhus was confined geographically to the Asia Pacific region, but now distributed in the tsutsugamushi triangle.

The patient usually presents with Eschar, a vesicular lesion at mite feeding site. Other complications are fever, maculopapular rash on trunk, and spreading to limbs. Serious one in the form of myocarditis, pneumonia, meningoencephalitis, jaundice acute renal failure, gastrointestinal bleeding, and even acute respiratory distress syndrome may develop.

The fever and eschar supported the diagnosis, which was confirmed serological by Scrub Typus IgM antibodies. The patient was improved by doxycycline injections. Doctors must be aware of zoonotic bacterial infections, which are easily treatable on early diagnosing.

Keywords: Malaysia, Scrub typhus, IgM antibodies, tsutsugamushi disease.

Introduction

While *Orientia tsutsugamushi* causing scrub typhus caused was confined geographically to the Asia Pacific region, a billion people are at risk and nearly a million cases were reported every year (Watt and Parola, 2003). *O. tsutsugamushi* is primarily distributed throughout the Asia Pacific rim. Scrub typhus is endemic in Korea, China, Vietnam, Taiwan, Japan, Pakistan, India, Sri Lanka, Thailand, Malaysia, and the tropical northern regions of Australia (Bonell *et al,* 2017). Serologic and molecular evidence of scrub typhus have also been identified in Africa and the Middle East (Izzard *et al,* 2010). Scrub typhus mortality rates ranged from < 1% to 50% depending on proper antibiotic treatment, individual immunity infected, and the *O. tsutsugamushi* strain (Chakraborty and Sarma, 2017). Rickettsial phospholipase A2 appears to be involved as a mediator of entry into host cells with subsequent release from phagosomes and injury to the host cell (Walker *et al,* 2001). However, infection with one strain does not prevent reinfection with a different strain (Choi *et al,* 2014)

The first scrub typhus Malaysian case was described in the early 1900s by Dowden as "kedani fever" or hairy mite (Yuhana *et al,* 2022). There is a disparity between the low reported incidence of scrub typhus and the high prevalence of antibodies to Rickettsia tsutsugamushi in rural population of Malaysia. Scrub typhus was found to be very common, causing 23% of all febrile illnesses at one hospital. The infection was particularly prevalent in oil palm workers, causing an estimated 400 cases annually in a population of 10,000 people living on one plantation. Clinical syndrome with failed sero-diagnosis was difficult to diagnose scrub typhus from other infections (Brown *et al,* 1976). Generally, human diseases caused by order Rickettsiales agents can range from mild (asymptomatic) to lethal, with flu-like (fever, headache, myalgia) in symptomology; during se-

vere infections, complications such as meningitis, intravascular complications, severe pneumonitis/peritonitis, and/or cardiac distress were reported (Biggs, 2016).

Tay *et al.* (2003) in Malaysia did seroprevalence for O. *tsutsugamushi* (OT), *R. typhi* (RT) and TT118 spotted fever group rickettsiae (SFGR) among 240 blood donors and febrile patients in urban areas reported 5.4%, 9.2% & 1.7% had either present or previous exposure to OT, RT and SFG rickettsiae, respectively. They added that patients admitted to an urban hospital had seropositive of OT (43.5%) and RT (22.9%), as compared to SFGR (11.6%). Antibody levels suggestive of active scrub typhus, murine typhus and tick typhus infections were found in 16.8%, 12.7% & 8.2% respectively. Ernieenor *et al.* (2021) highlighted the need of a large-scale close study of *O. tsutsugamushi* DNA sequences from chiggers that could be collected from other positive scrub typhus localities to precisely provide distribution and prevalence of this zoonotic pathogen.

A case report: Eight years 6-month-old Malay girl without underlying medical illness presented with an on-and-off fever associated with chills and rigor for 5 days relieved with syrup paracetamol and antibiotics given by a general practitioner. The fever relapsed a few hours after the effect of Paracetamol$^{(R)}$, with neither specific pattern of fever nor seizure. A day after the fever a maculopapular rash appeared on the upper limbs and gradually progressed to both lower limbs within 5 days of the fever onset, sparing the palm and the trunk, associated with pruritus, loss of appetite, weight loss of 1 kg, Lethargic.

Also, the child had a Runny nose for 1 day, shortness of breath, mild chest pain not associated with palpitation, bitemporal headache, and no syncopal attack. However, she denied having any sick contact, none around her had neither the same symptoms nor any irritability. Normal urine and stool output, she was staying near a palm oil plantation, and play with cats and birds. The sore throat started 2 days before admission. Also, a small painful pustule as mosquito bite over her right lower chest wall started 2 weeks before fever progressively getting larger discharging pus. She applied cream locally to soothe the pain. The skin lesion slowly dries off and forms a dry scab, with no similar skin lesions elsewhere. No history of any hospital admission, or known food or drug allergies, normal development history. All vaccinations were up to date; the last vaccination was taken at the age of 7 years old.

On physical examination the child was conscious and responsive; however, she looked lethargic, without respiratory distress. On examination, there were maculopapular rashes noted over her both upper and lower limbs, sparing the palm and trunk of the body. On examination of the mouth, the right tonsil was enlarged and bilateral palpable, non-tender cervical lymph nodes, and axillary lymph nodes. Inguinal lymph nodes were not palpable.

Anthropometric measures: Height: 125cm (btw 25th&50th percentile), weight: 22.3kg (btw 10^{th}&25^{th} percentile) and BMI: 14.27 kg/m^2 (btw 10^{th} &25^{th} percentile. Vital signs on admission: BP was 100/70 mmHg, pulse rate was 121/minute, temp. was 38.7°C, respiratory rate was 24breaths/min, and SpO_2 was 99% under room air.

Respiratory examination: there was mildly reduced air entry bilaterally over the lower zone. A vesicular breath sound was heard. No added sound was heard and normal cardiovascular examination. Arterial blood gas under a high-flow mask (10L/min) was normal. Abdominal examination showed soft, not distended, with tenderness over epigastric region. Only liver was 5cm palpable.

Laboratory examination: CBC and blood serology were carried out.

Results

Blood serology: Scrub typus IgM and *Mycoplasma pneumoniae* were positive. The rapid Dengue NS1, and dengue IgM, IgG, as well as other tests were negative.

The patient started IV C penicillin50000

u/kg (1.10 Mega unit QID), Second day she was given Doxycycline® 2mg/kg BD (50mg BD) for 7 days, five days later she was given Ceftriaxone® 1.1g OD (50mg/kg).
Details were given in tables (1 & 2) and figure (1).

Table1: Patient's complete CBC

Parameter	Range/ Unit		Reference
WBC	3.29 X 10^9/L	Low	4.5 -13.5
RBC	4.35 X 10^{12}/L		4.0- 5.2
HGB	110 g/L	Low	115- 135
HCT	33.0%	Low	35- 45
MCV	75.9fL	Low	77- 85
MCH	25.3pg	Low	26- 34
PLT	67.0 X 10^9/L	Low	170- 450
Neutrophils	62.3%		40.0- 80.0
Lymphocytes	32.2%		20.0- 40.0
Eosinophils	0%	Low	1.0- 6.0
Basophils	0.6 %		0.0- 2.0
Neutrophils	2.05%		1.8-8.0
Lymphocytes	1.06 X 10^9/L	Low	1.5- 6.5
Inflammatory marker/ CRP	47.3 mg/l	High	0- 0.5

Table 2: Patient serological examinations

Test done	Results
Scrub Typus IgM	Positive
Scrub typhus IgG	Negative
Endemic Typhus IgM	Negative
Endemic Typhus IgG	Negative
Tick Typhus IgM	Negative
Tick Typhus IgG	Negative
Chikungunya	Not detected
Melioidosis serology	Not detected
Mycoplasma pneumoniae	Positive
Dengue Virus serotyping	Negative
Leptospira IgM	Negative
NPA virus	Negative
Urine C&S	No growth
Blood C&S	No growth

Discussion

Generally speaking, *O. tsutsugamushi* is primarily distributed throughout the Asia Pacific rim. Scrub typhus is endemic in Korea, China, Taiwan, Japan, Pakistan, India, Thailand, Malaysia, and in the tropical (northern) regions of Australia (Currie *et al,* 1993). Scrub typhus has also been reported in Chile (Balcells *et al,* 2011); three cases were identified between 2015 and 2016 (Weitzel *et al,* 2016). Other reports include a case of scrub typhus in patients who were infected with *O. tsutsugamushi* while in West Africa (Ghorbani *et al,* 1997), and a patient from Dubai who developed infection with a new species *O. chuto* with similar nucleotide sequence to *O. tsutsugamushi* (Izzard *et al,* 2010). Zhang *et al.* (2013) reported that although most scrub typhus cases occurred in rural areas among farmers, so many cases were acquired in sett ings such as suburban Bangkok, where seroprevalence more than 20% and urban ones in Beijing and Seoul. Taylor *et al.* (2015) reported that accurate surveillance data on the scrub typhus incidence were not available because a diagnosis was not confirmed, overlooked, or confused with other endemic febrile illnesses. But, some experts have estimated that up to 1 million annual cases in the south-eastern Asia. Scrub typhus is not transmitted directly from person to person; it is only transmitted by the bites of vectors (Horton *et al,* 2016). Also, the mite vector (Morsy, 2012) and the scrub fever were reported in Egypt (El Sayed *et al,*

2018). Scrub typhus in clinically indistinguishable from malaria, dengue fever, other rickettsioses, leptospirosis, and enteric fever, which are common cause of acute unknown fever in the Asia-Pacific Countries (Kundavaram *et al,* 2013). The vectors of *Orientia tsutsugamushi* were once thought to be confined to an area designated as tsutsugamushi triangle. But, scrub typhus caused by *Orientia* species other than *O. tsutsugamushi* well beyond the limits of the Tsutsugamushi Triangle have triggered as to global presence of scrub typhus (Luce-Fedrow *et al,* 2018).

Clinically, both malaria and dengue fever Chikungunya resembles dengue but is milder and self-limiting, often with a rash share some common clinical features and similar endemic patterns with scrub typhus (Ahmad et al, 2016). Leptospirosis is a common disease in some tropical regions where scrub typhus also occurs. In a study of 296 febrile Thai patients, 69 patients (23%) had leptospirosis; 57 patients (19%) had scrub typhus and 12 patients (4%) had evidence of coinfection with leptospira and *O. tsutsugamushi* (Phimda *et al,* 2007). In Thailand, Laos, and Bangladesh, bordering Myanmar, have shown that scrub typhus and other rickettsial infections were among the leading fever causes in local communities (Yuhana *et al,* 2022). But, Korean elderly patients showed more severe complications compared with patients >16 years (Jang *et al,* 2014).

In the present study, a painless papule appeared at the bite site, with subsequent central necrosis in turn leads to the characteristic eschar with a black crust. This agreed with Audhya *et al.* (2015) in India, who reported that one or more eschars may develop before the onset of systemic symptoms without possibly a typical black crust. In adult patients, eschars must be overlooked if a careful clinical exam (including inspection of genitalia and skin folds under breast) was not performed (Berman and Kundin, 1973).

In the present study, an on-and-off fever associated with chills and rigor for 5 days relieved with syrup paracetamol and antibiotics given by a general practitioner. Fever relapsed within few hours without specific pattern or seizure. A day later a maculo-papular rash appeared on upper limbs and gradually progressed to both lower limbs within 5 days of the fever onset, sparing the palm and the trunk, associated with pruritus, loss of appetite, weight loss of one kg, Lethargic. She had a runny nose for one day, shortness of breath, mild chest pain, but without palpitation, bitemporal headache, and no syncopal attack. CDC (2024) reported that symptoms of scrub typhus usually begin within ten days after infection. Signs and symptoms include: Fever and chills, headache, body aches and muscle pain, a dark, scab-like area (eschar) at the mite bite site, mental changes, ranging from confusion to coma, enlarged lymph nodes and rash. They added that if not treated appropriately, scrub typhus can be fatal and may lead to organ damage and severe bleeding. Mortality rates varied widely by location and were increased in older patients, as presence of myocarditis, delirium, pneumonitis, and relationship between the rickettsial DNA levels in blood samples at admission time (Huang *et al,* 2018).

In the present study, there were scrub typus IgM and *Mycoplasma pneumoniae* positivity. Most patients with severe illness develop thrombocytopenia; elevations in hepatic enzymes, bilirubin, and creatinine may also be present. Most of the cases have normal white blood cell count, but Leukopenia or leucocytosis can occur (Rana *et al,* 2017). Besides, an eschar biopsy and/or PCR were not indicated. Reller *et al.* (2020) reported that in very low bacteremia, optimal sensitivity of qPCR for these rickettsioses required use of larger volumes of input DNA that could be achieved by improved extraction of DNA from blood and/or extraction of DNA from a larger initial volume of blood.

In the present study, treatment was initiated as soon as possible for any suspected or confirmed scrub case. Delayed treatment associated with the development of major organ dysfunction. Drugs administered was

doxycycline (200mg orally/intravenously twice daily for one day), followed by 100mg orally/intravenously twice daily for up to 7 days course. Azithromycin (500mg daily for five to seven days) is a good alternative to doxycycline for patients with mild to moderate disease. Rajapakse *et al.* (2017) Sri-Lanka, reported that awareness of these unusual manifestations will hopefully guide clinicians towards diagnosing the condition early, and initiating early appropriate antibiotics and other supportive measures

Conclusion

Scrub typhus represents an important and under-recognized cause of acute febrile illness (AFI), and requires careful diagnosing.

Treatment using doxycycline or azithromycin is beneficial. Doctors should be aware of zoonotic bacterial infections as Rickettsial illnesses, which are easily treatable but only if infection is recognized early.

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References

Ahmad, S, Dhar, M, Mittal, G, Bhat, NK, Shirazi, N, *et al,* 2016: A comparative hospital-based observational study of mono- and co-infections of malaria, dengue virus and scrub typhus causing acute undifferentiated fever. Eur. J. Clin. Microbiol. Infect. Dis. 35, 4:705-11

Audhya, M, Abirami, D, Srikanth, S, 2015: Atypical eschar: An unusual cutaneous manifestation of scrub typhus. J. Vector Borne Dis. 52: 267-72.

Balcells, ME, Rabagliati, R, García, P, *et al,* 2011: Endemic scrub typhus-like illness, Chile. Emerg. Infect. Dis, 17:1659-66.

Berman, SJ, Kundin, WD, 1973: Scrub typhus in South Vietnam: A study of 87 cases. Ann. Intern. Med. 79:26-34.

Biggs, HM, 2016: Diagnosis and management of tickborne rickettsial diseases: Rocky mountain spotted fever and other spotted fever group rickettsioses, ehrlichioses, and anaplasmosis, in United States. MMWR. Recomm. Rep. 65:1-44.

Bonell, A, Lubell, Y, Newton, PN, Crump, JA, Paris, DH, 2017: Estimating the burden of scrub typhus: A systematic review. PLoS Negl. Trop. Dis. 11, 9:e0005838. doi: 10.1371/journal.pntd. 0005838.

Brown, GW, Robinson, DM, Huxsoll, DL, Ng, TS, Lim, K, 1976: Scrub typhus: A common cause of illness in indigenous populations. Trans. R. Soc. Trop. Med. Hyg. 70, 5/6:444-8.

CDC, 2024: Typhus Fever: About Scrub Typhus https://www.cdc.gov/typhus/about/scrub.html.

Chakraborty, S, Sarma, N, 2017: Scrub typhus: An emerging threat. Indian J. Dermatol. 62, 5:478-85.

Choi, S, Jeong, HJ, Ju, Y, Gill, B, Hwang, KJ, *et al,* 2014: Protective immunity of 56-kDa type -specific antigen of *Orientia tsutsugamushi* causing scrub typhus. J. Microbiol. Biotechnol. 24, 12:1728-53

Currie, B, O'Connor, L, Dwyer, B, 1993: A new focus of scrub typhus in tropical Australia. Am. J. Trop. Med. Hyg. 49:425-30.

El Sayed, I, Liu, Q, Wee, I, Hine, P, 2018: Antibiotics for treating scrub typhus. Cochrane Database Syst. Rev. 9, 9:CD002150. doi: 10.1002/14651858.CD002150.pub2.

Ernieenor, FCL, NorJaiza, MJ, Fadillah, A, Canedy, J, *et al,* 2021: Screening and genotyping of *Orientia tsutsugamushi* from field-collected on-host chiggers (Acari: Prostigmata) recovered from a positive scrub typhus locality in Kelantan, Malaysia. Exp. Appl. Acarol. 84, 1:171-82.

Ghorbani, RP, Ghorbani, AJ, Jain, MK, Walker, DH, 1997: A case of scrub typhus probably acquired in Africa. Clin. Infect. Dis. 25:1473-9.

Horton KC, Jiang J, Maina A, *et al,* 2016: Evidence of *Rickettsia* and *Orientia* infections among abattoir workers in Djibouti. Am. J. Trop. Med. Hyg. 95, 2:462-5.

Huang, MH, Juan, YH, Chen, YT, 2018: Prolonged coma in a scrub typhus patient. International journal of infectious diseases: IJID: Official publication of Inter. Soc. Infect. Dis. 77:5-7.

Izzard, L, Fuller, A, Blackwell, S, *et al*, 2010: Isolation of a novel *Orientia* species (*O. chuto* sp. nov.) from a patient infected in Dubai. J. Clin. Microbiol. 48:4404-9.

Jang, MO, Kim, JE, Kim, UJ, *et al,* 2014: Differences in the clinical presentation and the frequency of complications between elderly & non-elderly scrub typhus patients. Arch. Gerontol. Geriatr. 58: 196-204.

Kundavaram, AP, Jonathan, AJ, Nathaniel, S

D, Varghese, GM, 2013: Eschar in scrub typhus: A valuable clue to the diagnosis. J. Postgrad. Med. 59, 3:177-8.
Luce-Fedrow, A, Lehman, MN, Kelly, DJ, Richards, AL, *et al,* 2018: A review of scrub typhus (*Orientia tsutsugamushi* and related organisms): Then, now, and tomorrow. Trop. Med. Infect. Dis. 3, 1:8.doi: 10.3390/tropicalmed3010008.
Phimda, K, Hoontrakul, S, Suttinont, C, *et al,* 2007: Doxycycline versus azithromycin for treatment of leptospirosis and scrub typhus. Antimicrob. Agents Chemother. 51:3259-68.
Rajapakse, S, Weeratunga, P, Sivayoganathan, S, Fernando, SD, 2017: Clinical manifestations of scrub typhus. Trans. R. Soc. Trop. Med. Hyg. 111, 2:43-54.
Rana, A, Mahajan, SK, Sharma, A, Sharma, S, Verma, BS, *et al,* 2017: Neurological manifestations of scrub typhus in adults. Trop. Doct. 47:22-5.
Reller, ME, Dumler, JS, 2020: Optimization & evaluation of a multiplex quantitative PCR assay for detection of nucleic acids in human blood samples from patients with spotted fever rickettsiosis, typhus, rickettsiosis, scrub typhus, monocytic ehrlichiosis, and granulocytic anaplasmosis. J. Clin. Microbiol. 58, 9:e01802-19.
Tay, ST, Kamalanathan, M, Rohani, Y, 2003: Antibody prevalence of *Orientia tsutsugamushi, Rickettsia typhi*, and TT118 spotted fever group rickettsiae among Malaysian blood donors and febrile patients in the urban areas. Southeast Asian J. Trop. Med. Publ. Hlth. 34, 1:165-70.
Taylor, AJ, Paris, DH, Newton, PN, 2015: A systematic review of mortality from untreated scrub typhus (*O. tsutsugamushi*). PLoS Negl. Trop. Dis. 9, 8:e0003971. doi:10.1371/j. pntd.
Walker, DH, Feng, HM, Popov, VL, 2001: Rickettsial phospholipase A2 as a pathogenic mechanism in a model of cell injury by typhus & spotted fever group rickettsiae. Am. J. Trop. Med. Hyg. 65, 6:936-42.
Watt, G, Parola, P, 2003: Scrub typhus and tropical rickettsioses. Curr. Opin. Infect. Dis. 16:29 -36.
Weitzel, T, Dittrich, S, López, J, *et al,* 2016: Endemic Scrub Typhus in South America. N. En-gl. J. Med. 375:954-60.
Yuhana, MY, Hanboonkunupakarn, B, Tanganuchitcharnchai, A, *et al*, 2022: Rickettsial infections are neglected causes of acute febrile illness in Teluk Intan, Peninsular Malaysia. Trop. Med. Infect. Dis. 7, 5:77. doi:10.3390/tropicalmed7050077.
Zhang, WY, Wang, LY, Ding, F, *et al,* 2013: Scrub typhus in mainland China, 2006-2012: The need for targeted public health interventions. PLoS Negl. Trop. Dis. 7:e2493.

Explanation of figure

Fig.1: Localized necrotic skin lesion (eschar) at mite (chigger) bite site.