

Melioidosis and scrub typhus co-infection in a patient presenting with acute undifferentiated febrile illness

Muhamad Yazli Yuhana^{*1,2}, Ampai Tanganuchitcharnchai³, Pimpan Sujariyakul³, Piengchan Sonthayanon⁴, Kesinee Chotivanich⁴, Daniel H. Paris^{5,6}, Sasithon Pukrittayakamee¹, Stuart D. Blacksell^{3,7}, Borimas Hanboonkunupakarn¹

¹Department of Clinical Tropical Medicine, Faculty of Tropical Medicine, Mahidol University, Bangkok 10400, Thailand

²Infectious Diseases Unit, Department of Internal Medicine, Universiti Teknologi MARA, Sungai Buloh 47000, Selangor, Malaysia

³Mahidol-Oxford Tropical Medicine Research Unit, Faculty of Tropical Medicine, Mahidol University, Bangkok 10400, Thailand

⁴Department of Molecular Tropical Medicine and Genetics, Faculty of Tropical Medicine, Mahidol University, Bangkok 10400, Thailand

⁵Swiss Tropical and Public Health Institute, Basel, Switzerland

⁶University of Basel, Basel, Switzerland

⁷Centre for Tropical Medicine, Nuffield Department of Clinical Medicine, Churchill Hospital, Oxford, United Kingdom

Case Report

ABSTRACT

ARTICLE INFO

Keywords:

Scrub typhus,
Melioidosis,
Co-infection,
Malaysia

*Corresponding author:

aleeyuhana@hotmail.com

DOI: 10.20885/JKKI.Vol10.Iss1.art12

History:

Received: April 10, 2018

Accepted: March 29, 2019

Online: April 30, 2019

Copyright ©2019 Authors.
This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International Licence (<http://creativecommons.org/licenses/by-nc/4.0/>).

Melioidosis and scrub typhus are endemic diseases in Malaysia. However, unlike melioidosis, scrub typhus is more difficult to be diagnosed and in Malaysia its true disease burden is unknown. We report a case of severe melioidosis and scrub typhus co-infection in a patient living in a small village in Peninsular Malaysia whom presented with fever and headache. This case highlights the importance of considering scrub typhus as a diagnostic possibility in cases of acute undifferentiated febrile illness in rural areas such as that of in Peninsular Malaysia.

Melioidosis dan scrub typhus merupakan penyakit endemik di Malaysia. Scrub typhus lebih sulit didiagnosis dibandingkan dengan melioidosis. Usaha sistematis dan ilmiah untuk mengukur besarnya perbandingan health loss (disease burden) dari scrub typhus belum diketahui hingga saat ini. Kami melaporkan kasus koinfeksi melioidosis berat dan scrub typhus pada pasien yang tinggal di sebuah desa kecil di Semenanjung Malaysia yang mengalami demam dan sakit kepala. Kasus ini menyoroti pentingnya mempertimbangkan scrub typhus sebagai kemungkinan diagnostik dalam kasus penyakit demam akut yang tidak berdiferensiasi di daerah pedesaan seperti di Semenanjung Malaysia.

INTRODUCTION

Melioidosis which is caused by non-lactose fermenting gram-negative rods, *Burkholderia pseudomallei* is a typical environmental community-acquired febrile illness in Malaysia.¹ Scrub typhus, on the other hand, is caused by

the obligately intracellular organism, *Orientia tsutsugamushi*, is transmitted via bites from the larvae of Trombiculid mites; known as chiggers to humans. The bites may elicit eschars in which if present may assist in early clinical recognition.²

³ Both melioidosis and scrub typhus may cause

severe infections with multiorgan dysfunctions such as pneumonitis, meningitis, septic shock and death.⁴⁻¹⁰ Unlike melioidosis, scrub typhus remains an under-appreciated and under-diagnosed disease, likely due to non-specific clinical presentation and the laborious nature of its diagnostic requirements.^{11,12} We describe a patient who had presented with undifferentiated febrile symptoms with acute kidney injury who had initially been diagnosed with melioidosis before a co-infection of scrub typhus was made.

Case report

During the rainy season in May 2016, a 60-year-old Malay man from Teluk Intan, Perak (Northwest of Peninsular Malaysia) complained of 7 days of fever which was associated with a headache. He had no vomiting, visual complaints, confusion or neck pain. He was a farmer working on paddy fields. There was no report of recent travel and involvement in forest activities. His medical history included poorly controlled type 2 diabetes mellitus with recent Hba1c of 10.8%.

On physical examination, he was alert and enterily orientated. His vital signs include an oral temperature of 39°C, blood pressure of 110/77 mmHg with the pulse rate of 100 beats per minute, respiratory rate of 18 breaths per minute with oxygen saturation of 98% on room air, with total qSOFA scores of 0 (13). Skin examination was unremarkable with no visible eschars seen. Eyes were normal, and there were no palpable cervical lymph nodes, mouth ulcers or myositis elicited. The cardio-respiratory examination was unremarkable and abdominal examination failed to demonstrate organomegaly. Central nervous system examination did not isolate any focal neurological abnormalities.

The initial laboratory parameters demonstrated leukocytosis with white cell counts of 20.2×10^9 cell/L (reference range $4.0-12.0 \times 10^9$ cell/L) and platelet of 252×10^9 cell/L (reference range $150-440 \times 10^9$ cell/L). He was not known to have chronic kidney disease and his serum creatinine level was markedly elevated at 561 $\mu\text{mol/l}$ (reference range 62-106

$\mu\text{mol/L}$) with normal liver enzymes with alanine aminotransferase of 27 IU/L (reference range 10-50 IU/L) and aspartate aminotransferase of 42 IU/L (reference range 10-40 IU/L) and normal total bilirubin level of 7.9 $\mu\text{mol/l}$ (reference range $< 21 \mu\text{mol/l}$). C-reactive protein (CRP) was elevated at 154 mg/l (reference range $< 5\text{mg/l}$).

Blood culture taken on admission showed the presence of non-lactose fermenter Gram-negative bacillus that was later identified as *Burkholderia pseudomallei* by Vitek 2 Compact (BioMerieux, Inc. USA). Antibiotic susceptibility test by disc diffusion method showed resistant to ceftazidime and susceptible to imipenem. Thorax and abdominal computed tomography scans were normal with no evidence of lungs or intraabdominal abscesses. Despite imipenem, he remained febrile on the ward. Serum MAT for leptospirosis and PCR targeting the LipL32 gene in Leptospiral were both negatives. Dengue NS1 and IgM by ELISA and blood film for malaria were non-reactive as well. Patient's serum was tested positive using the InBios Scrub Typhus Detect IgM Rapid Test which later was confirmed by nucleic acid detections assays by polymerase chain reaction using the forward primer (AACTGATTTTATTCAAACCTAATGCTGCT) and reverse primers (TATGCCTGAGTAAGATACRTGAATRGAATT) against the 47-kDa was positives with DNA copies of 1800 copies/ml.¹⁴ Doxycycline 200mg loading followed by 100mg twice a day was commenced. He became afebrile within 48 hours of starting with the anti rickettsial treatment. The patient completed 14 days of imipenem and seven days of doxycycline and with normalization of blood parameters and was subsequently discharged well (Figure 1).

Ethics statement

This study had been approved by the Malaysian National Medical Research and Ethics Committee (1 September 2015). Informed consent was signed by the patient.

RAGS 5/3 (59/2014), Dean-MORU School of Tropical Medicine Mahidol University Fund and the Wellcome Trust of the United Kingdom.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

Acknowledgement

We are grateful to the patient for his participation in this study and to the Teluk Intan Hospital laboratory and clinical team; Haryati Ishak, Baanumathi Chandran, Stephanie J. Peter, Nur Shahida Zainal and Muhammad Faez Ismail.

REFERENCES

- Nathan S, Chieng S, Kingsley PV, Mohan A, Podin Y, Ooi MH, et al. Melioidosis in Malaysia: Incidence, Clinical Challenges, and Advances in Understanding Pathogenesis. *Trop Med Infect Dis.* 2018;3(1).
- Lee SH, Kim DM, Cho YS, Yoon SH, Shim SK. Usefulness of eschar PCR for diagnosis of scrub typhus. *J Clin Microbiol.* 2006;44(3):1169-71.
- Kingston HW, Hossain M, Leopold S, Anantatat T, Tanganuchitcharnchai A, Sinha I, et al. Rickettsial Illnesses as Important Causes of Febrile Illness in Chittagong, Bangladesh. *Emerg Infect Dis.* 2018;24(4).
- Theunissen C, Cnops L, Van Esbroeck M, Huits R, Bottieau E. Acute-phase diagnosis of murine and scrub typhus in Belgian travelers by polymerase chain reaction: a case report. *BMC Infect Dis.* 2017;17(1):273.
- Malheiro L, Ceia F, Alves J, Carvalho AC, Sobrinho-Simoes J, Sousa R, et al. Severe interstitial pneumonia due to murine typhus in a patient returning from Bali. *IDCases.* 2017;9:17-20.
- Wulff J, Margolin J, Coleman NE, Demmler-Harrison G, Lam F, Shah MD. A Severe Case of Murine Typhus Presenting With Anemia and Severe Thrombocytopenia. *J Pediatr Hematol Oncol.* 2018;40(3):e185-e90.
- Sakamoto N, Nakamura-Uchiyama F, Kobayashi K, Takasaki T, Ogasawara Y, Ando S, et al. Severe murine typhus with shock and acute respiratory failure in a Japanese traveler after returning from Thailand. *J Travel Med.* 2013;20(1):50-3.
- Dittrich S, Rattanavong S, Lee SJ, Panyanivong P, Craig SB, Tulsiani SM, et al. *Orientia*, rickettsia, and leptospira pathogens as causes of CNS infections in Laos: a prospective study. *Lancet Glob Health.* 2015;3(2):e104-12.
- Stephens BE, Thi M, Alkhateb R, Agarwal A, Sharkey FE, Dayton C, et al. Case Report: Fulminant Murine Typhus Presenting with Status Epilepticus and Multi-Organ Failure: an Autopsy Case and a Review of the Neurologic Presentations of Murine Typhus. *Am J Trop Med Hyg.* 2018;99(2):306-9.
- Zueter A, Yean CY, Abumarzouq M, Rahman ZA, Deris ZZ, Harun A. The epidemiology and clinical spectrum of melioidosis in a teaching hospital in a North-Eastern state of Malaysia: a fifteen-year review. *BMC Infect Dis.* 2016;16:333.
- Paris DH, Dumler JS. State of the art of diagnosis of rickettsial diseases: the use of blood specimens for diagnosis of scrub typhus, spotted fever group rickettsiosis, and murine typhus. *Curr Opin Infect Dis.* 2016;29(5):433-9.
- Paris DH, Shelite TR, Day NP, Walker DH. Unresolved problems related to scrub typhus: a seriously neglected life-threatening disease. *Am J Trop Med Hyg.* 2013;89(2):301-7.
- Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA.* 2016;315(8):801-10.
- Jiang J, Chan TC, Temenak JJ, Dasch GA, Ching WM, Richards AL. Development of a quantitative real-time polymerase chain reaction assay specific for *Orientia tsutsugamushi*. *Am J Trop Med Hyg.* 2004;70(4):351-6.
- Afzal Z, Kallumadanda S, Wang F, Hemmige V, Musher D. Acute Febrile Illness

- and Complications Due to Murine Typhus, Texas, USA1,2. *Emerg Infect Dis.* 2017;23(8):1268-73.
16. Mayxay M, Castonguay-Vanier J, Chansamouth V, Dubot-Peres A, Paris DH, Phetsouvanh R, et al. Causes of non-malarial fever in Laos: a prospective study. *Lancet Glob Health.* 2013;1(1):e46-54.
 17. Paris DH, Chattopadhyay S, Jiang J, Nawtaisong P, Lee JS, Tan E, et al. A nonhuman primate scrub typhus model: protective immune responses induced by pKarp47 DNA vaccination in cynomolgus macaques. *J Immunol.* 2015;194(4):1702-16.
 18. Wangrangsimakul T, Althaus T, Mukaka M, Kantipong P, Wuthiekanun V, Chierakul W, et al. Causes of acute undifferentiated fever and the utility of biomarkers in Chiangrai, northern Thailand. *PLoS Negl Trop Dis.* 2018;12(5):e0006477.
 19. Newton PN, Keolouangkhhot V, Lee SJ, Choumlivong K, Sisouphone S, Choumlivong K, et al. A prospective, open-label, randomized trial of doxycycline versus azithromycin for the treatment of uncomplicated murine typhus. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America.* 2018.
 20. Phimda K, Hoontrakul S, Suttinont C, Charonwat S, Losuwanaluk K, Chueasuwanchai S, et al. Doxycycline versus azithromycin for treatment of leptospirosis and scrub typhus. *Antimicrob Agents Chemother.* 2007;51(9):3259-63.