Hong Kong College of Physicians
Case report for Interim Assessment
Specialty Board of Advanced Internal Medicine (AIM)

For AIM Training, case reports should be submitted in the prescribed format together with the application form for Interim Assessment at least EIGHT Weeks before the date of Interim Assessment

Name of candidate (print and sign): Cheung Hoi Ting Heidi
Hospital and Unit: PWH/Medical Specialty: Geriatrics and AIM
Name of supervisor (print and sign): Dr Howan Leung
Date(s) and place (hospital) of patient encounter: 3/2023 - PWH
Date of report submission: 5/9/2023

Case report

Note: Failure to follow the prescribed format (including the number of words) results in a FAILURE mark (score between 0 and 4) for the Case Report.

Title: A case of Rickettsial infection and its diagnostic challenges

Case history:

Ms. A was a 44 old lady with good past health who presented with one week history of fever. She attended her private general practitioner (GP) and was prescribed paracetamol, diclofenac and dimendydrinate. She had ongoing swinging fever and developed a rash on her face, which spread to her trunk and limbs.

On further history taking, miss A went hiking in the mountains 2 days prior to onset of fever in Hong Kong. Upon admission, Miss A's blood pressure was 110/80mmHg, and had a temperature of 39.5 degree Celsius, and tachycardia with heart rate of 100 beats per minute. On examination, she had hepatomegaly, bilateral conjunctivitis and erythematous papular eruption over face and upper body. The rash was painless and was not pruritic. There was no mucosal involvement. A 1cm eschar was noted at right groin (figure 1). On examination, she had cervical lymphadenopathy and hepatomegaly. Her abdomen was non tender. Initial investigations revealed acute kidney injury with creatinine elevated to 210 umol/L. Her leukocyte count was normal, but she had a decreased platelet count of 109 x10^9/L. Her liver function was deranged, with alkaline phosphatase up to 263 UI/l and aspartate aminotransferase up to 125 U/l. Bilirubin was normal.

Viral hepatitis tests were all negative. USG abdomen confirmed hepatomegaly (measuring 18cm at mid clavicular line). Intrahepatic ducts and common duct were not dilated. Her CXR was normal.

She was reviewed by the dermatology team and the impression was papular eruption due to infection. Ms. A was initially started on empirical intravenous ceftriaxone and doxycycline for treatment of atypical infection based on clinical presentation. Her blood culture and urine culture was negative. Subsequent investigations revealed that serology tests for cytomegalovirus, dengue, rubella and measles were negative. Orientia tsutsugamushi antibody was positive with rise of titre from 128 to 512. Ms. A's rash resolved and her fever subsided. Her renal and liver function improved significantly. She recovered fully after 7 days of doxycycline.

Discussion and literature review

Rickettsioses are diseases due to gram negative and obligate intracellular bacterium that belong to the genus Rickettsia. Humans can be infected either through bites or contact with faeces of an infected arthropod vectors, for example lice, fleas or ticks. It is usually divided into two groups; the spotted fever group (SFG) and the typhus group (TG) rickettsioses. The typus group can be further categorised into scrub typhus, urban typhus, and epidemic typhus. Scrub typhus and spotted fever are the most common types of rickettisal diseases in Hong Kong, followed by urban typhus. [1] For our patient, she was identified to have Orientia tsutsugamushi, which belongs to scrub typus. It is mainly transmitted by infected larval trombiculid mites in bushes and grasses.

Diagnosis of rickettsial infections is achieved through clinical history including exposure to potential source of rickettsial disease and laboratory testing. Presence of eschar aids clinical diagnosis of scrub typhus with specificity up to 98.9%. However it lacks applicability due to wide variation in distribution. [2] It is important to perform thorough physical examination as eschar can be found in hidden areas such as groin in our case, other common sites include neck, axilla, waist, and inguinal area. While the symptoms take 10 – 12 days for the chigger bite to appear, the incubation period can be anywhere between 6 days and 21 days.

Scrub typhus can manifest as fever, myalgia, anorexia and

lymphadenopathy. Severe infection includes meningoencephalitis, myocarditis, acute renal failure and septic shock. The mortality is up to 70% for untreated cases. [3]

Laboratory testing are more reliable in diagnosing scrub typhus, which can be divided into direct and indirect methods. Direct methods include isolation and culturing of bacteria and DNA-based diagnosis by identifying different genetic markers by PCR. Indirect methods involve detection of antibodies propagate as a result of humoral immunity against O. tsutsugamushi. Weil-felix agglutination reaction is the oldest test in current use in Hong Kong. It is inexpensive and result are available in 1-2 days. It detects IgM antibody against different Proteus antigens such as OX10, OXK, and OX2 that cross-respond with rickettsiae. [4] However it has low specifity and sensitivity due to the use of non- rickettsial antigen for agglutination. It is still widely used in initial screening for developing countries.

Immunofluorescence assay (IFA) was considered gold standard for detection of rickettsial infection due to its high sensitivity and specificity. However, it has been outranked by other techniques such as enzyme-linked immunosorbent assay (ELISA) with similar sensitivity and specificity but with lower cost. ELISA based methods identifies IgM and IgG antibodies in serum samples for the detection of Orientia tsutsugamushi. It does not require paired sampling (unlike IFA, which requires a difference of 14 days in both sampling events), and is therefore better for early detection of scrub typhus. IgM antibodies can be detected after the 1st week of infection, while IgG antibodies appear at the end of the 2nd week. [5]

Direct method of diagnosis include bacterial isolation and culture but this method is time-consuming and requires high biosafety level facility for culturing of Orientia tsutsugamushi. Another direct testing method is polymerase chain reaction based detection method. It is highly specific and sensitive for detecting rickettsial infection and is particularly useful in early stages of infection when antibody levels may still be low. PCR based detection methods uses genetic markers such as 56kDa tsa and GroEL. [6] The choice of laboratory test depends on the clinical presentation and timing of sample collection, therefore a combination of serology testing, PCR and clinical correlation is often used to establish a definitive diagnosis of rickettsial infections in Hong Kong.

Doxycycline and azithromycin are treatment options against scrub typhus. However, there were reported cases of possible doxycycline resistant strains. Studies have shown that Tigecycline, a semi-synthetic tetracycline derivatives, is effective to work against strains resistant to doxycycline. It has excellent tissue-drug concentration, with high ratio of intracellular to extracellular ratio, making it effective in treating intracellular bacteria like O. tsutsugamushi. Lee et al showed that Tigecycline has better antibiotic efficacy than doxycycline, which might be applied to severe scrub typhus cases. [7]

Delayed recognition and therapy increases the morbidity and mortality. The clinical presentation of fever with eschar or rash with recent rural exposure should facilitate the diagnosis and initiation of treatment of rickettsial infection. This case report highlights the importance of early cognition and prompt treatment of rickettsial infection. Laboratory testing helps aid the diagnosis but should be chosen wisely according to the timing of presentation and test availability.

Tables and figures (where applicable) (no more than two figures)

Figure 1. 1cm eschar at right groin

Reference (not more than 10)

1. Centre for Health Protection, Department of Health - Typhus and other rickettsial diseases. Centre for Health Protection. (n.d.) https://www.chp.gov.hk/en/healthtopics/content/24/45.html
2. 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; 89:301–307.
3. Taylor AJ, Paris DH, Newton PN. A systematic review of mortality from untreated scrub typhus (Orientia tsutsugamushi). PLoS Negl Trop Dis. 2015;9:e0003971.
4. Sanap SS, Thakur VA, Maniar JM, Vasave SV, Vaidya SP. Weil-Felix test-a diagnostic tool for rickettsial diseases. Austin J Clin Pathol 2017; 4:1046–1049.
5. Rahi M, Gupte M, Bhargava A, Varghese GM, Arora R. DHRICMR guidelines for diagnosis and management of rickettsial diseases in India. Rickettsiales. Springer, Berlin, 2016; pp 125–133.
6. Husin NA, AbuBakar S, Khoo JJ. Current tools for the diagnosis and detection of spotted fever group Rickettsia. Acta Trop. 2021 Jun;218:105887.
7. Lee SM, Kwon HY, Im JH, Baek JH, Hwang SS, Kang JS, Chung MH, Lee JS. In Vitro Activity of Tigecycline Against Orientia tsutsugamushi. Yonsei Med J. 2016 Jul;57(4):1034-7.

No of words in Case History and Discussion (excluding references):___1066_____

(should be between 1000-2000)

Declaration

I hereby declare that the case report submitted represents my own work and adheres to the prescribed format. I have been in clinical contact with the case selected. The case report has not been submitted to any assessment board or publication and it is NOT related to my second specialty(ies), if any. My consent is hereby given to the College to keep a copy of my case report, in written and/or electronic, at the College Secretariat and allow the public to have free access to the work for reference.

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(signature of Trainee)

Endorsed by Supervisor *

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(signature of Supervisor)

* Supervisors must go over the Case Report with the Trainees, advise Trainees whether further amendments are necessary, review the Originality/Similarity Report prepared by Trainees, adherence to the required format, sign on the report and remind Trainees on issues related to copyright and plagiarism.