CP Ng 吳忠波
CB Lo 盧志彪
KK Wong 黃君強
CH Chung 鍾展鴻

A returned traveller with persistent fever due to murine typhus

外遊後持續發熱——鼠型斑疹傷寒症的病例報告

Murine (endemic) typhus is a notifiable disease in Hong Kong, but its diagnosis can be difficult. We report a case of murine typhus in a middle-aged man who presented with persistent fever, headache, and skin rash 2 weeks after returning from a visit to China. The diagnosis of murine typhus requires a high index of suspicion for a febrile patient with a history of potential exposure to the disease vector (rat flea) in an endemic area. The importance of early recognition lies in the potential for early therapeutic intervention, leading to decreases in morbidity and duration of stay in hospital.

在香港，地方性鼠型斑疹傷寒是一種需要申報的疾病，但此病難以診斷。我們報告了一宗中年男性患上鼠型斑疹傷寒的病例；他從中國大陸旅遊回港兩週後呈現持續發燒、頭痛和出現皮疹。醫生應對於那些曾在疫區有可能接觸病菌媒介(如老鼠跳蚤)的發燒病人提高警覺。早期識別此病的重要性在於可以盡早治療，以減少發病率和住院時間。

Introduction

Murine (endemic) typhus, first recognised as a distinct entity in 1926, remains an endemic zoonosis worldwide, particularly in warm climates with heavy populations of rat or opossum reservoirs and flea vectors.[1-3] Murine typhus is a notifiable disease in Hong Kong. Since the clinical features are often non-specific, clinicians should maintain a high index of suspicion for murine typhus. Missing the diagnosis can result in significant morbidity and mortality.[4] We report on a patient who presented to North District Hospital with murine typhus.

Case report

A 54-year-old man developed fever 2 weeks after returning from a 2-day holiday in China. He became unwell with fever, rigors, throbbing headache, and cough. He was initially seen by a general practitioner and treated for upper respiratory tract infection with minimal improvement.

He attended the Accident and Emergency Department of North District Hospital in July 2001 because of persistent fever and severe headache for 5 days. On examination, he had a temperature of 37.8°C, blood pressure of 135/75 mm Hg, and pulse rate of 100 beats/minute. Respiratory, cardiovascular, and abdominal examinations showed no abnormalities, except that the throat was congested. Neurological examination was unremarkable and no meningeal signs were detected. No rash or joint swelling was detected. Chest X-ray showed clear lung fields. In view of the persistent fever and headache, the patient stayed in the observation room for close monitoring. For 8 hours during observation, the fever persisted and the headache was not improved by analgesia. Since preliminary investigations showed mild thrombocytopenia and deranged liver function, the patient was subsequently admitted to the Department of Medicine for further management. Once there, his fever went up from 37.8°C to 39°C. Physical examination was unremarkable, except for the appearance of a transient erythematous macular rash over the trunk on the day after admission.

Key words:
Disease vectors, endemic diseases;
Fever;
Typhus, endemic flea-borne

關鍵詞：
病菌媒介，地方病；
發燒；
斑疹傷寒，地方性蚤傳

Hong Kong Med J 2002;8:457-9

North District Hospital, 9 Po Kin Road, Sheung Shui, Hong Kong:
Accident and Emergency Department
CP Ng, FRCS (Edin), FHKAM (Emergency Medicine)
CB Lo, FHKAM (Emergency Medicine), FHKAM (Paediatrics)
CH Chung, FHKAM (Emergency Medicine), FHKAM (Surgery)
Department of Medicine
KK Wong, FHKCP, FHKAM (Medicine)

Correspondence to: Dr CP Ng

Table 1. Results of preliminary investigations

Investigation	Results Level (normal range)
Haemoglobin (g/dL)	13.6 (13.4-17.2)
White cell count (x 10^9 /L)	5.7 (3.9-10.7)
Platelets (x 10^9 /L)	112 (152-358)
Erythrocyte sedimentation rate (mm/h)	25 (0-15)
Sodium (mmol/L)	132 (135-145)
Potassium (mmol/L)	4.0 (3.5-5.1)
Urea (mmol/L)	6.0 (3.5-8.1)
Creatinine (mmol/L)	90 (75-110)
Total bilirubin (mmol/L)	15 (5-20)
Alanine aminotransferase (U/L)	173 (10-57)
Aspartate aminotransferase (U/L)	203 (16-41)
Lactate dehydrogenase (U/L)	21 (213-395)
Albumin (g/L)	31 (35-50)
Blood culture	No growth
Urine culture	No growth
Stool culture	No growth
Sputum culture	No growth

The results of the preliminary investigations are shown in Table 1. Laboratory investigations revealed thrombocytopenia, elevated erythrocyte sedimentation rate, hyponatraemia, and hypoalbuminaemia, together with elevated serum activities of liver transaminases and lactate dehydrogenase.

For 3 days after admission, the patient continued to have fever and headache. His temperature was 39°C, despite empirical oral amoxicillin/clavulanic acid. The patient was investigated further for pyrexia of unknown origin. Subsequent enquiries revealed that he had travelled to the village of Foshan in Guangdong province of China for 2 days. He could not recall any insect, tick, or flea bite. There was no history of handling dead rats, but the patient described the sanitary facilities at the place where he had visited as being poor. Fever started about 2 weeks after he returned from China. No eschar was found on his body.

Lumbar puncture showed clear cerebrospinal fluid with normal biochemistry. Cultures for bacteria, tuberculosis, and parasites were all negative. Plain computed tomography scan of the brain was normal. Infectious screening for hepatitis, atypical pneumonia, malaria, typhoid, and brucella were all negative. Ultrasound of the abdomen showed small gallstones only. The results of the Weil-Felix agglutination test were reported 1 week later—Proteus OX-19 was greater than 1:1280; both OX-2 and OX-K were 1:20. In view of the temporal relationship between travel and symptom onset, together with the supportive evidence of biochemical changes, the provisional diagnosis at this juncture was murine typhus.

The patient was prescribed oral doxycycline 100 mg twice daily for 1 week and his fever subsided 3 days after treatment was started. Later, indirect immunofluorescent antibody test against *Rickettsia typhi* confirmed the diagnosis of a recent murine typhus infection. The patient recovered and was discharged 2 weeks after admission. The disease was notified to the Department of Health, Hong Kong.

Discussion

Murine typhus is a zoonotic infection caused by *R typhi*. Murine typhus is endemic in many parts of the world, particularly the Indian subcontinent, South-East Asia, the Americas, the Russian Federation, Africa, and the Mediterranean countries.[5,6] It is a flea-borne disease and is transmitted by the oriental rat flea (*Xenopsylla cheopis*). Humans are infected incidentally from the bites of fleas that are infected. Fleas are infected with *R typhi* from feeding on an acutely ill rat. *Rickettsia typhi* multiplies in the gut of the flea and is excreted in the faeces. When feeding on humans, the flea defecates and rickettsia-contaminated faeces can be inoculated into skin abrasions by scratching the bitten area, leading to human infection. The incubation period ranges from 6 to 14 days.

Data from the Department of Health in Hong Kong show an increasing number of notifications of typhus fever. From January 1990 to September 2001, there were a total of 87 reported cases (Table 2).[7] This is, however, likely to be an underestimate of the true incidence in view of the non-specific clinical features of the disease.[4,8]

Common imported infections, including malaria and typhoid fever, are usually considered by clinicians as a differential diagnosis in travellers returning from endemic areas. Murine typhus is, however, difficult to diagnose clinically since it resembles other common diseases such as influenza. This case illustrates the importance of considering some less common imported infections, such as rickettsial infections in travellers returning from endemic areas. A history of exposure to the rat flea vector is a crucial aid in the diagnosis, although a history of such exposure is frequently absent or seldom recalled in infected patients, as illustrated in this case.

The triad of fever, headache, and rash has traditionally been used as a clinical diagnostic tool in rickettsial diseases, including murine typhus.[9] These three signs and symptoms were simultaneously present in this patient, but studies have shown that this is only the case in half of all infected patients.[10] Accordingly, the absence of any of the above features should not dissuade one from considering a diagnosis of murine typhus.

Table 2. Number of notifications of typhus fever in Hong Kong (1990-2001)

Year	No. of cases
1990	1
1991	0
1992	6
1993	8
1994	6
1995	7
1996	5
1997	9
1998	9
1999	26
2000	4
2001 (Jan-Sep)	6

Some simple laboratory tests can help suggest the diagnosis in the correct clinical setting. Common laboratory findings are hyponatraemia, thrombocytopenia, hypoalbuminaemia, elevated erythrocyte sedimentation rate, and elevated liver transaminases.[9,11,12] These abnormalities were present in this patient. Thus, the presence of thrombocytopenia in a febrile patient with evidence of hepatic injury and flea exposure in an endemic area would suggest the possibility of murine typhus. The Weil-Felix agglutination test usually becomes positive after approximately 5 days of the illness. The disease commonly induces a high titre to Proteus OX-19, with lower or negative titres to OX-2 and OX-K. This test is not specific,[4,13] however, and the diagnosis requires confirmation through demonstration of the presence of rickettsia-specific antigens in complement fixation, agglutination, radioimmune precipitation, or indirect fluorescent antibody tests.

Management of murine typhus depends on early diagnosis. The preferred antibiotic therapy is tetracycline, doxycycline, or chloramphenicol. Quinolones may be suitable alternatives.[14] Although patients usually become afebrile within 3 days, treatment should be continued for 2 to 3 days longer to prevent relapse.

Conclusion

This case illustrates several key features of the diagnosis of murine typhus—a disease with which clinicians in Hong Kong may not be familiar. Murine typhus should, however, be included as a differential diagnosis for patients presenting with pyrexia of unknown origin, with a history of travel or residence in an endemic area, and with possibility of contact with rat fleas in that area. This is especially important when the temporal relationship between the time of travel and symptom onset is compatible. Understanding the characteristic laboratory findings may help in the detection and prompt response to this poorly recognised endemic zoonosis. Early diagnosis and treatment result in decreases in morbidity and duration of stay in hospital.

References

1. Dumler JS. Murine typhus. Semin Pediatr Infect Dis 1994;5:137-42.
2. Irons JV, Bohls SW, Thurman DC, et al. Probable role of the cat flea, *Ctenocephalides felis*, in transmission of murine typhus. Am J Trop Med Hyg 1944;24:359-62.
3. Farhang-Azad A, Traub R, Sofi M, Wisseman CL Jr. Experimental murine typhus infection in the cat flea, *Ctenocephalides felis* (Siphonaptera: Pulicidae). J Med Entomol 1984;21:675-80.
4. Choi KW. Case reports and review on typhus. Bulletin of the Hong Kong Society for Infectious Diseases 2000;4:22-3.
5. Schriefer ME, Sacci JB Jr, Dumler JS, Bullen MG, Azad AF. Identification of a novel rickettsial infection in a patient diagnosed with murine typhus. J Clin Microbiol 1994;32:949-54.
6. Hassan IS, Ong EL. Fever in the returned traveller. Remember murine typhus! J Infect 1995;31:173-4.
7. Public Health and Epidemiology Bulletin. Hong Kong: Department of Health; 1990-2001.
8. French GL, Vallance-Owen J, Woo ML. Scrub typhus at the Chinese University of Hong Kong. J Hong Kong Med Assoc 1985;37:191-2.
9. Dumler JS, Taylor JP, Walker DH. Clinical and laboratory features of murine typhus in south Texas, 1980 through 1987. JAMA 1991;266: 1365-70.
10. Whiteford SF, Taylor JP, Dumler JS. Clinical, laboratory, and epidemiologic features of murine typhus in 97 Texas children. Arch Pediatr Adolesc Med 2001;155:396-400.
11. Taylor JP, Betz TG, Rawlings JA. Epidemiology of murine typhus in Texas. 1980 through 1984. JAMA 1986;255:2173-6.
12. Stuart BM, Pullen RL. Endemic (murine) typhus fever: clinical observations of 180 cases. Ann Intern Med 1945;23:520-36.
13. Bassett DC, Ho AK, Tam JS, Lam LY, Cheng AF. The laboratory diagnosis of rickettsial diseases in Hong Kong. J Trop Med Hyg 1992; 95:327-30.
14. Raoult D, Drancourt M. Antimicrobial therapy of rickettsial diseases. Antimicrob Agents Chemother 1991;35:2457-62.