MURINE TYPHUS : A FORGOTTEN CAUSE OF FEBRILE ILLNESS IN SINGAPORE

K C Loh, Y S Leo, M K Heng, B C Goh

ABSTRACT

We report 6 cases of murine typhus presented to us within a period of 3 months. The diagnoses were made based on the Weil-Felix reaction in the context of supportive clinical and epidemiological features, and response to appropriate antimicrobial therapy. This review serves to remind us that murine typhus is still an important cause of acute febrile illness in Singapore, especially among the migrant Indian workers.

Keywords: *endemic typhus, Rickettsia typhi, clinical features, evaluation, treatment.*

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INTRODUCTION

Murine typhus has been described as "a good example of a disease whose importance is inadequately appreciated - except by the patient, and, even today, in most parts of the world, he will never know what ails him because the diagnosis will not be made." This statement made by Traub et al[1] still holds true today.

As a zoonosis involving peridomestic rats and ecto-parasites, murine typhus is endemic in South-east Asia[2-6]. However, with the high standard of public health and living condition enjoyed by Singaporeans over the years, the disease has become an unfamiliar entity to most of us. Our recent spate of cases were reported mainly among the migrant workers living in overcrowded and unhygienic quarters. We will emphasise on the epidemiologic and clinical aspects of the illness in our context, together with a review of the literature.

PATIENTS AND METHODS

Diagnosis of murine typhus was made on the basis of a positive serology with Weil-Felix reaction using commercial Proteus OX-K and OX-19 antigens (Wellcome Diagnostics, UK). Such patient show a four-fold rise in convalescent titre or a single titre of 1:320 or greater in Proteus OX-19 antibody[7]. All the cases showed negative titre to Proteus OX-K antigen. Type or species specific serology was not available in our laboratory for diagnosis. The cases reported here represent all 6 of the cases seen in our department within a 3-month period from February to April 1994.

Department of General Medicine
Tan Tock Seng Hospital
Moulmein Road
Singapore 308433

K C Loh, M Med (Int Med), MRCP (UK)
Registrar

M K Heng, MBBS
Medical Officer

B C Goh, M Med (Int Med), MRCP (UK)
Medical Officer (Specialist)

Communicable Disease Centre
Tan Tock Seng Hospital

Y S Leo, M Med (Int Med), MRCP (UK)
Senior Registrar

Correspondence to: Dr K C Loh
c/o Division of Endocrinology & Metabolism
Department of Medicine
Dalhousie University
5303 Morris Street
Halifax, Nova Scotia
Canada, B3J 1B6

CASE REPORTS

Case 1

A previously healthy 37-year-old male Indian national was admitted with a one-week history of fever associated with chills, rigors and profuse sweating. He also complained of arthralgia, myalgia, and cough with yellowish sputum. He has been working here for 3 years as a brick-layer at the construction site. He lived with his fellow migrant workers in a make-shift quarters at the work-site which was infested with rats.

On admission, the patient was febrile with a temperature of 39.8°C but otherwise comfortable and non-toxic looking. There was no cutaneous rash, lymphadenopathy, viscero-megaly, or other abnormal physical findings. Haematological investigation showed normal leucocyte count (TW 7,800/μL) with monocytosis of 18% (normal range 2-10%) and a low platelet count of 97,000/μL. The erythrocyte sedimentation rate (ESR) was 53mm/hr. The liver function test showed mild transaminitis (ALT 185U/L, AST 142U/L). Extensive septic workout including blood and urine cultures, blood film for malarial parasites, chest roentgenogram, hepatitis serology and Widal test were all negative. However, the Weil-Felix reaction showed a positive titre of greater than 1:640 to Proteus OX-19 antigen. The patient was then promptly started on oral tetracycline with defervescence of fever within 12 hours.

Case 2

A previously healthy 27-year-old male Indian national presented with similar complaints of fever associated with chills and rigors, and generalised arthralgia and myalgia of a week's duration. He also had headache and unproductive cough. He was a room-mate of Case 1 and he has been working at the same site as a welder for 2 years.

The patient was febrile (40°C) but non-toxic looking. There was relative temperature-pulse dissociation (pulse rate of 80-90 per minute) throughout the febrile period. Clinical examination was normal apart from mild hepatosplenomegaly. Haematologic indices were normal apart from mild monocytosis (TW 5,300/μL with 10% monocytes, platelet 157,000/μL). Septic workout and other investigations were done as in Case 1 and showed negative results. The initial Weil-Felix reaction to Proteus OX-19 antigen showed a titre of 1:40 which rose to 1:640 after a week's interval. During the interim period additional diagnostic tests including serologic tests for *Pseudomonas pseudomallei* and brucellosis,

autoimmune markers, bone marrow biopsy and ultrasonography of the hepatobiliary system were performed. The results were all negative. The patient was started on oral tetracycline on day 8 of admission with prompt defervescence of fever within 24 hours.

Case 3

A 28-year-old Bangladeshi male presented with one-week history of fever with chills and rigors, cough with whitish sputum, and frequent vomiting after meals. There was no headache, photophobia or other complaints. He worked as a construction worker in Singapore for 3 years and resided at the work site.

The patient was febrile (temperature spike of 40.4°C) and tachycardic but otherwise non-toxic in appearance. There were no abnormal signs apart from mild hepatomegaly. The leucocyte count was 10,200/μL with 12% monocytes and the platelet count was 262,000/μL. ESR was 46mm/hr. Liver function test showed transaminitis (ALT 78U/L, AST 85U/L). Results of septic workout as in previous cases were negative. The Weil-Felix test was back on the fifth hospital day with a positive Proteus OX-19 antibody titre of >1:640. The patient was started on oral doxycycline 100mg om with prompt lysis of fever within 6 hours.

Case 4

A 69-year-old Indian, male, Singaporean was admitted in a febrile and confused state. He had been ill for 10 days with fever and headache. His family was in India and he lived alone in an old shop-house and worked as an assistant in a grocery shop. He had a history of non-insulin dependent diabetes and heavy alcohol consumption.

The patient was febrile and disoriented on admission. Physical examination revealed a generalised erythematous maculopapular rash over the trunk and mild hepatosplenomegaly. Initial laboratory investigation showed thrombocytopenia (platelet count 58,000/μL) and coagulopathy (prothrombin time 16 sec, control 11 sec; activated partial thromboplastin time 36 sec, control 28 sec) which was attributed to alcoholic liver cirrhosis with hypersplenism. Liver function test revealed hypoalbuminaemia (Alb 27g/L) and elevated transaminases (ALT 47U/L, AST 123U/L). He was started on empiric antibiotic cover with intravenous ceftriaxone 1 g om and oral doxycycline 100mg bid after the septic workout. However, he deteriorated clinically into severe septic shock on the third hospital day with blood pressure reading of 80/60mmHg. The blood indices showed a disseminated intravascular coagulation state with worsening coagulopathy (PT 18 sec, aPTT 69 sec, TCT 23sec), elevated D-dimer and soluble fibrin monomer levels, and severe thrombocytopenia (platelet count 10,000/μL). The patient was managed with inotropic support, regular plasma infusion and platelet transfusion of up to a total of 21 units over the next 4 days.

The putative diagnosis then was Dengue shock syndrome but this was proven wrong by the negative serology. The septic workout results including cultures of specimens obtained from the patient's blood, urine, sputum, stool and cerebrospinal fluid were all negative. Other investigations with non-yielding results included malarial screen, typhoid and leptospiral serology, computerised axial tomography of the brain, and ultrasonography of the hepatobiliary system. The initial Weil-Felix reaction showed a Proteus OX-19 antibody titre of 1:80 which rose to more than 1:640 in the convalescent specimen taken 2 weeks later. The patient came out of the shock but had persistent niggling fever till the tenth hospital day. Oral doxycycline was continued for 2 weeks and he was well upon discharge.

Case 5

A previously healthy 33-year-old male Bangladeshi presented with a 6-day history of fever with chills and rigors, bitemporal headache, myalgia and arthralgia. He has been working here for the past 3 years as a soil-tester. He lived in the company's quarters which was infested with rats.

The patient was febrile (40°C) but otherwise comfortable, with a dissociated pulse rate of 80-90 per minute. Clinical examination was normal apart from mild splenomegaly. Haematological indices were normal apart from elevated monocyte count of 15%. Liver function test showed elevated transaminases (ALT 107U/L, AST 75U/L). Routine septic workout was unyielding. The initial Widal Weil-Felix reaction were negative with all titres being < 1:40. A repeat Weil-Felix reaction done a week later showed an elevation of Proteus OX-19 titre to 1:160. He was then promptly started on oral doxycycline 100mg om and the fever defervesced within a day.

Case 6

A previously healthy 35-year-old male, Indian national was admitted for a 10-day history of fever with chills and rigors, headache, and myalgia. He has been working here for 2 years as an artisan and he stayed at the construction site.

The patient was febrile (40°C) but otherwise well with no abnormal clinical findings. Haematological indices were normal apart from mild monocytosis of 13%. Liver enzymes were mildly raised (ALT 65U/L, AST 72U/L). The diagnosis was made on the fourth hospital day when the Weil-Felix test showed an elevated Proteus OX-19 titre of 1:320. Doxycycline tab 100mg om was started with defervescence of fever after 24 hours.

DISCUSSION

The Typhus group of diseases are febrile illnesses caused by Rickettsial organisms that are often transmitted to humans by vectors. Epidemic (louse-borne) typhus is an infection with *Rickettsia prowazekii* transmitted by the human body louse. This is associated with a severe illness and high case-fatality rate if untreated. Murine (endemic or flea-borne) typhus is a zoonosis caused by *Rickettsia typhi* and communicable from rodent hosts to humans sporadically by means of the rat flea. This is a milder and shorter-lasting disease, with lower case-fatality rate. Both forms share an antigen with Proteus OX-19. Scrub typhus, however, shares an antigen with Proteus OX-K and is caused by infection with *Rickettsia tsutsugamushi*. This form is transmitted by the bite of larval trombiculid mites and characterised by the presence of eschar and regional lymphadenitis. Other forms of Rickettsial diseases such as the spotted fever group are not seen in our region. Typhus was a notifiable disease in Singapore until 1976. Epidemic typhus had not been reported. Murine and scrub typhus were notified from time to time. Our report of 6 cases in a 3-month period in our department alone portends an important phenomenon as compared with a total of 43 locally contracted murine typhus cases reported during the period 1968-1976[8].

There had been considerable interest in typhus fever in this region, especially during the second world war and the Vietnam conflict. Despite the waning interest after these events, the disease continues to have significant impact, accounting for 10-20% of hospital admissions for acute febrile illness in some parts of Thailand and Malaysia[6,9,10]. The

crowding of our cases among the migrant workers who live in unhygienic quarters is not surprising. All our cases were considered to be indigenous as the migrant workers have arrived here for 2-3 years without leaving the country. The infections were most likely to be acquired locally due to poor living conditions. In our previous record of locally contracted cases of typhus fever by Goh[8], the majority of them contracted the disease at their place of work or in their rural home surroundings where rodent infestation was prevalent. An outbreak of murine typhus was noted among Khmer refugees living at an evacuation site with high rodent population on the Thai-Kampuchean border in 1986[11]. It continued to be a major health problem in Thai-Kampuchean border camps with increased incidence during the dry season[5]. However, murine typhus can also be a disease of urban setting as described variously in Texas[12-14] and Los Angeles County[15] in the United States. In the suburban setting of the Los Angeles County, the reservoir was traced to infected domestic cats and opossums[15].

It is interesting to note that all our cases were of similar ethnic origin, despite the substantial population of migrant workers of other ethnicity. This observation was also reported by Goh[8], with the Indians having an ethnic-specific morbidity rate of 5.1 per 100,000 as compared with 2.3 and 2.0 per 100,000 for the Chinese and Malays respectively. We could not ascertain if this was related to their inherent susceptibility or living habits. All our cases were males, which could be biased by the male-dominated occupations wherein our cases were reported. A significantly higher incidence rates among the males were also noted in our previous study by Goh with a male to female ratio of 7:1. In the outbreak amongst the Khmers reported by Brown et al[11], the incidence rate among the males was 6/1,000 as compared with 3.9/1,000 in the females. Taylor et al, however, found no differences in incidence between the sexes in a study of 200 cases in Texas from 1980-1984[13]. The disease can affect all age groups, though it is most commonly seen in the those in the third and fourth decades of life, as in our cases although there might be an inherent age bias in our migrant workers. In a study of 320 children with one-week or longer history of obscure fever admitted to a hospital in Thailand, 28 of them (8.7%) were diagnosed to have typhus fever[6].

The diagnosis of this disease is often made serologically. However, a high index of suspicion can often be made based on the symptoms, effectiveness of tetracycline therapy and the presence of a large rat population. A therapeutic trial of tetracycline might be considered worthwhile before the serology result is back if the index of suspicion is high, as this would effectively reduce the morbidity, length of hospital stay, and expense of elaborate laboratory investigations as were illustrated in our cases. Such a practice has been commonly adopted in rural areas with the absence of sophisticated laboratory support[5]. Specific serodiagnosis for typhus could be obtained with indirect fluorescent antibody test[16] and its micromodification[17] which yield highly sensitive and specific results. An indirect immunoperoxidase test has also been developed as a viable, practical substitute for use in rural areas where there is no fluorescence microscope[18-20]. Unfortunately, we are still relying on the traditional Weil-Felix test. Though simple to perform, this test has been shown to be neither sensitive nor specific in the serodiagnosis of rickettsial diseases, yielding false positive results with leptospirosis, malaria, Proteus infections, and other febrile illnesses[16,21]. The Proteus OX-19 antibody which we used to diagnose murine typhus would also be raised in other rickettsial infections, such as the Rocky Mountain spotted fever, epidemic typhus, and tick typhus. Although far from ideal, we could nonetheless assume such seropositive cases to be murine typhus in the proper clinical setting as cases of the Rocky Mountain spotted fever are reported in the Western hemisphere only while the epidemic and tick typhus have not been reported locally thus far. Our experience showed that an initial negative Weil-Felix reaction performed after one week of febrile illness does not exclude the diagnosis of typhus and further elaborate tests may not be immediately necessary apart from repeating the serology which may be carried out earlier at one instead of the usual two-week interval in the suspected patients who are otherwise well clinically.

The route of rickettsial transmission is often uncertain. The rat flea Xenopsylla cheopis has been imputed as the classical vector for murine typhus as it was found to be prevalent on commensal rats in many endemic areas. Various other kinds of arthropods, such as rat lice, cat fleas and mites have been suggested as vectors[1,2,15,22]. The most likely route of transmission considered by most authors have been contact of breached skin with infective faeces or crushed fleas. Other possible means include the feeding process of infected fleas, or inhalation of dried faeces[1,22]. We could not ascertain the vector in our cases. None of our patients had obvious breach of the integument or history of flea or rat bite. Similarly in the Thai series of 137 cases of murine typhus there was no history of flea bite and infrequent history of direct contact with rats[23]. In the Texas series, only 26% of the patients recalled a flea bite before the onset of symptoms and 29% noted rodents present in the household or surrounding environment[13]. Suburban typhus cases in the Los Angeles County were found to be more likely than neighbourhood controls to own a cat or dog[15]. Clustering of cases in single household were rare but was seen in our Cases 1 and 2. This could possibly be related to innate immunity or subclinical infection.

Of the various rickettsial infections, murine typhus is a relatively milder febrile illness with practically negligible mortality[24,25]. However, there were sporadic case reports of murine typhus with significant morbidity. These include the complications of endocarditis[26], spontaneous splenic rupture[27], meningitis or encephalitis[28], and renal impairment[29]. All but one of our cases were relatively well despite hectic fever at presentation and throughout the course of the illness. Our only local patient went through a tempestuous course with septic shock. This underscores the fact that it can be fraught with significant potential morbidity and even mortality in certain vulnerable groups of patients, as in our case of an elderly patient who was already debilitated by diabetes and alcoholism. However, as we lack specific serodiagnosis, we could not rule out the possibility of Proteus infection or even epidemic typhus in this case. Mortality from murine typhus occurred in 1% of the Texas series[13] and 1.5% of a Thai series[23]. The clinical features in our cases were similar to most reported series[6,8,11-14,23]. The most common symptom being fever of 1-2 weeks' duration, with chills and rigors. Two of our patients were noted to have temperature-pulse dissociation as classically seen in typhoid fever. Other common symptoms include myalgia and arthralgia, headache, cough, anorexia, vomiting and malaise. None of our patients had neurological complications. The only common clinical signs in our cases were mild hepato- and/or splenomegaly, which were seen in 3 of the 6 patients; while rash was noted in 1 patient only. Of the 20 patients treated at the Middleton Hospital in Singapore during the period 1968-1975, hepatomegaly was found in 18(90%), splenomegaly in

17(85%), and cutaneous rash in 11(55%) of the patients respectively[8]. In a review of 137 cases in Thailand, Silpapojakul et al reported hepatomegaly in 24% and rash in 20% of the cases; complications were rare but included jaundice, pneumonia, renal insufficiency and meningitis[23]. The Khmer series recorded palpable splenomegaly in fewer than half of the patients; and rashes, which were usually subtle, in fewer than a quarter of the patients[11]. Rash on the trunk or limbs was more commonly reported in the West, affecting 54% to 57% of patients in 2 reviews of 80 and 200 murine typhus patients, respectively in Texas[13,14]. This is probably due to the fair complexion of the Caucasians which allows the usually mild rash to be more visible.

We found certain haematological and biochemical features worth mentioning in our cases. There was high incidence of increased monocyte population (11-18%) with a normal leucocyte count and a reduced platelet count. All our patients also exhibited some elevation of liver enzymes. None of our patients developed anaemia, jaundice, or azotemia. Amongst the laboratory parameters, the south Texas series found disease severity to be related to leucocytosis, hypoalbuminaemia and azotemia[14]. In the setting of fever, rat-infested living conditions and transaminitis, it is paramount to exclude leptospirosis by serology and culture tests.

Tetracycline has been regarded as the treatment of choice for rickettsial disease[30,31]. Chloramphenicol has become less popular because of the higher incidence of toxic side-effects as well as relapse after treatment[32]. A single 200mg dose of doxycycline had been shown to significantly reduce the duration of fever, with 79% of patients so treated becoming afebrile in 48 hours as compared to 15% in untreated group[23]. With the exception of Case 4, all our cases showed prompt defervescence of fever within 24 hours of tetracycline therapy. In pregnant women, there have been anecdotal reports of good therapeutic response with erythromycin[33]. The duration of hospitalisation ranged from 6-16 days, with most patients being discharged within 48 hours of initiation of tetracycline therapy. None of our cases showed evidence of relapse when reviewed 2 weeks post discharge from hospital.

CONCLUSION

Murine typhus will continue to be an important cause of acute febrile illness in Singapore with our present increasing numbers of migrant workers. Apart from the need to improve the living conditions of these workers; there is a cogent need for our physicians to be acquainted with this illness, and our laboratories to acquire specific serodiagnostic tools than to rely on the non-specific Weil-Felix test. By adopting a vigilant approach and starting empirical treatment of suspected cases with tetracycline early, we could help in significant cost-savings by reducing hospitalisation days and avoiding elaborate and expensive diagnostic tests as were performed in our cases.

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