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Murine Typhus in Southern Taiwan during 1992–2009

Ko Chang,† Yen-Hsu Chen,† Nan-Yao Lee, Hsin-Chun Lee, Chun-Yu Lin, Jih-Jin Tsai, Po-Liang Lu, Tun-Chieh Chen, Hsiao-Chen Hsieh, Wei-Ru Lin, Ping-Chang Lai, Chia-Ming Chang, Chi-Jung Wu, Chung-Hsu Lai, and Wen-Chien Ko*

Department of Internal Medicine, Kaohsiung Medical University, Medical College, Kaohsiung, Taiwan; Department of Internal Medicine, Kaohsiung Municipal Hsaio-Kang Hospital, Kaohsiung, Taiwan; Departments of Internal Medicine and Graduate Institute of Clinical Medicine, National Cheng Kung University College of Medicine and Hospital, Tainan, Taiwan; Institute of Infectious Diseases and Vaccinology, National Health Research Institutes, Miaoli, Taiwan; Department of Internal Medicine, Tian-Sheng Memorial Hospital, Pingtung, Taiwan; Division of Infectious Diseases, Department of Internal Medicine, E-Da Hospital/I-Shou University, Kaohsiung, Taiwan

Abstract. Clinical information regarding murine typhus in Taiwan is limited. In this study, 81 cases of serologically documented murine typhus during 1992–2009 at four referral hospitals in southern Taiwan were analyzed. There was a significant correlation between average environmental temperature and case numbers of murine typhus (r = 0.747, P = 0.005). Acute hepatitis was found in 67% of cases, and hyperbilirubinemia (serum total bilirubin ≥ 23.9 μmol/L) was found in 38%. The intervals between the initiation of appropriate therapy to defervescence were longer in patients with hyperbilirubinemia than those without hyperbilirubinemia (6.1 versus 4.1 days; P = 0.015). Nine (11.1%) showed development of severe illnesses such as acute respiratory distress syndrome (2 patients), aseptic meningitis (3), and acute renal failure (4). Only one died of acute respiratory distress syndrome. Cases of murine typhus were often found during the summer and had acute febrile hepatitis. Those patients with hyperbilirubinemia tended to have a delayed recovery even with appropriate therapy.

INTRODUCTION

Endemic murine typhus, which is caused by *Rickettsia typhi*, is a worldwide zoonosis. The rat flea, *Xenopsylla cheopis,* is the main vector, and rodents and arthropods are natural reservoirs. The possible routes of transmission are flea bites, contamination of excoriated skin, and inhalation of contaminated aerosols. In humans, murine typhus often manifests as an acute febrile illness with a rash,[1,2] and protean clinical manifestations such as acute hepatitis, pneumonia, meningitis or in combination, have been reported in many countries. For example, aseptic meningitis is more common in the United States,[1] Thailand,[3] Tunisia,[4] Israel,[5] Spain,[6] and Greece,[7,8] and acute biochemical hepatitis is more common in Thailand and Laos.[9,10] Kidney involvement has been reported in Spain[11] and Israel.[12]

A previous study reported 505 cases of murine typhus in Taiwan in 1961,[13] However, it only reported clinical features and cases were not confirmed serologically. The predominant manifestation of murine typhus in southern Taiwan has been reported to be acute febrile illness with rash.[14] However, there have been no epidemiologic surveys of murine typhus in Taiwan. Therefore, we analyzed the clinical characteristics and prognosis of 81 cases of murine typhus in southern Taiwan.

MATERIALS AND METHODS

The medical charts of cases of murine typhus serologically documented at four major referral hospitals in southern Taiwan during 1992–2009 were reviewed. Seven cases previously reported were also included in the present study.[14] The diagnoses of murine typhus, scrub typhus, and Q fever were confirmed by the Center for Disease Control (Taipei, Taiwan) according to the serologic profile, which required at least a four-fold increase in IgG titers against *R. typhi* between acute-phase and convalescent-phase serum samples, or a significant serum IgM titer (≥ 1:80) measured by immunofluorescence assay.[11] All serum samples were also tested for specific antibodies against *Coxiella burnetii* (Q fever) and *Orientia tsutsugamushi* (scrub typhus). The diagnosis of acute Q fever or scrub typhus was based on the presence of compatible symptoms and signs and serologic profiles, as described.[15]

Clinical information, including demographic data, exposure history, laboratory data, clinical course, and prescribed antimicrobial therapy, was obtained from medical records. The mean environmental temperature during 1981–2010, obtained from the Central Weather Bureau (Taipei, Taiwan) (http://www.cwb.gov.tw/V7/climate/monthly Mean/Taiwan_tx.htm [in Chinese]) was used to represent the outdoor temperature during the study period, and this value was put into a correlation analysis. Fever was defined as an axillary body temperature ≥ 38°C, and fever for ≥ 14 days was regarded as being a prolonged fever.

Acute hepatitis was defined as an increase in serum aminotransferases levels ≥ 1.5 times the upper limit of reference values, i.e., aspartate aminotransferase ≥ 60 U/L or alanine aminotransferase (ALT) ≥ 78 U/L.[16] Hyperbilirubinemia was defined as serum levels of total bilirubin ≥ 23.9 μmol/L. Defervescence was defined as an axillary body temperature < 37.5°C for three consecutive days. The disappearance of constitutional symptoms was regarded as a clinical response to antimicrobial therapy. A patient with a heart rate < 110 beats/minute in conjunction with a high fever (≥ 38.9°C), in the absence of cardiac arrhythmia, pacemaker or beta-blocker agents, was considered as having relative bradycardia.[14]

Acute renal failure was defined by an increase in the serum creatinine level ≥ 44.2 μmol/L (0.5 mg/dL) if the baseline level was > 221 μmol/L (2.5 mg/dL), or an increase in the serum creatinine level by > 20% if the baseline level was > 221 μmol/L, or if there was a need for acute renal replacement therapy.[17] A diagnosis of acute respiratory distress syndrome (ARDS) was defined by the presence of all of the

* Address correspondence to Wen-Chien Ko, Department of Internal Medicine, National Cheng Kung University Hospital and Medical College; #138, Sheng Li Road, Tainan 704, Taiwan. E-mail: winston@mail.ncku.edu.tw
† These authors contributed equally.

following criteria: 1) acute onset; 2) chest radiography showing bilateral lung infiltrates; 3) severe hypoxia with a partial pressure of arterial oxygen to fraction of inspired oxygen ratio (PaO_2/FiO_2) ≤ 200 mm of Hg, regardless of the level of positive end-expiratory pressure; and 4) no clinical evidence of increased left atrial pressure with a pulmonary arterial wedge pressure ≤ 18 mm of Hg.[18] Acute aseptic meningitis was diagnosed for cases with headache and lymphocytic pleocytosis or increased protein levels in cerebrospinal fluid (CSF) without bacterial growth. Persons with murine typhus complicated by ARDS, aseptic meningitis, or acute renal failure, were regarded as having severe complications of murine typhus.

Statistical analysis. The chi-square test or Fisher's exact test was used for categorical variables, and the Mann-Whitney U test was used for continuous variables. A P value < 0.05 was considered statistically significant and all tests were two-tailed. The degree of linear relationship of case numbers of murine typhus and average temperature (°C) per month was calculated by using the Pearson's correlation, and the correlation was taken to be significant at the level of 0.01 (two-tailed).

RESULTS

During 1992–2009, a total of 81 cases of murine typhus were identified in southern Taiwan. According to the Notifiable Infectious Diseases Statistics System in the Center for Disease Control, Taiwan, 136 documented cases were reported in southern Taiwan during 2003–2009. In our study, there were 62 cases in the same period,[19] accounting for 45.6% of 136 documented cases. Seventy-eight (96.3%) of the 81 patients had at least a four-fold rise in IgG titers, and 3 (3.7%) had an IgM titer > 1:80 in this study. A seasonal variation of murine typhus was noted, and the number of cases per month varied, ranging from 1 case in March to 17 cases in July. Most (35 of 81, 43.2%) were found during May–August, which is summer in Taiwan. A significant correlation was noted between monthly average temperature (°C) and number of cases of murine typhus (correlation coefficient = 0.747, P = 0.005, by Pearson's correlation), as shown in Figure 1.

The mean age of the patients was 50.0 years (range = 10–86 years). However, most patients were in their third to seventh decades of life (56 cases, 69.1%), as shown in Figure 2. The only pediatric case was in a 10-year-old child.

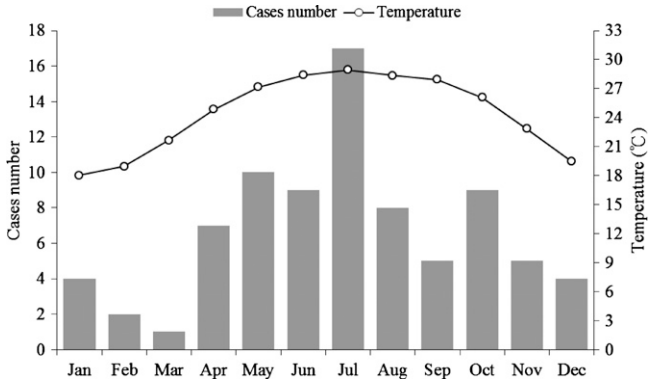

FIGURE 1. Monthly distribution of 81 cases of murine typhus in southern Taiwan, 1992–2009, and its correlation with mean environmental temperature of Tainan and Kaohsiung areas.

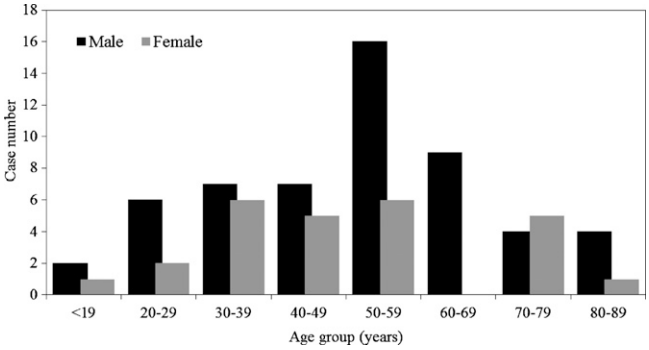

FIGURE 2. Age and sex distribution of 81 cases of murine typhus in southern Taiwan, 1992–2009.

The male-to-female ratio was 2.12:1 (55:26). Only one patient recalled having contact with mice in his living environment before the onset of disease. As for other possible occupational, household or recreational exposures to *R. typhi*, 6 were farmers, 6 patients recalled recent insect bites, 11 had recently been mountain climbing, and 17 had close contact with cats or dogs.

The initial manifestations of murine typhus were not specific enough to be suggestive of such a diagnosis, and included febrile illness (78 cases, 96.3%) accompanied with chills (49, 61.0%) or headache (42, 51.9%). Myalgia (23, 28.4%), rash (23, 28.4%), non-productive cough (21, 25.9%), joint pain (12, 14.8%), and bone pain (6, 7.4%) were also noted. Of 71 cases with available information, 48 (67.6%) had relative bradycardia. Of 40 cases with urinalysis data, 10 (25%) had microscopic hematuria. Pulmonary infiltrations on chest radiographs were noted in 15 (30.6%) of 49 cases. On the basis of abdominal sonographic results for 20 cases, 3 were found to have gall bladder wall thickening and 10 had fatty liver.

Of 74 cases with available serum biochemical results, 19 (25.7%) had normal serum levels of AST or ALT (≤ 50 U/L). At initial presentation, acute hepatitis was found in 52 (70.3%) patients, none of whom reported alcoholism. Serum ALT levels five times greater than normal levels were found in 9 (12.2%) of 74 cases. Of 51 cases, 36 (70.6%) had elevated serum levels of alkaline phosphatase (> 126 U/L), and 35 (87.5%) of 40 cases had elevated levels of lactate dehydrogenase (> 250 U/L) (Table 1). For coexisting viral hepatitis, surface antigen of hepatitis B virus was noted in 4 (9.5%) of 42 cases and antibodies to hepatitis C virus were noted in 2 (5%) of 40 cases.

Of 81 cases with complete blood cell counts, only 10 (12.3%) had leukocytosis (leukocyte count ≥ 12.0 × 10^9 cells/L), and 8 (13.6%) had leukopenia (≤ 4.0 × 10^9 cells/L). Nearly 75% of the 81 cases had normal leukocyte counts at initial presentation. Thrombocytopenia, defined as a platelet count < 100 × 10^9 cells/L, was present in 30 (37.0%) cases. In addition, prolongation of activated partial thromboplastin time (36 of 53, 67.9%) was noted more commonly than prolongation of prothrombin time (16 of 51, 31.4%). As found in bacterial infections, most (68 of 73, 93.2%) cases had increased serum levels of C-reactive protein (≥ 80 mg/L) (range = 5–2,700 mg/L).

Of 49 cases with available serum levels of total bilirubin, hyperbilirubinemia was found in 17 (34.7%) cases, and 10 (20.4%) cases had total bilirubin levels ≥ 34.2 μmol/L. No patients with cholestatic hepatitis had any clinical or radiologic

TABLE 1
Clinical characteristics and laboratory data for 81 patients with murine typhus in southern Taiwan, 1992–2009

Parameter	No. cases	Mean value	95% Confidence interval	Range
Age, years	81	50.0	46.1–54.0	10–86
Laboratory data at initial presentation				
Leukocytes, $\times 10^9$/L	81	7.73	6.9–8.6	1.4–23.7
Neutrophils, %	75	71.0	68–74.1	37–97
Hemoglobin, g/L	81	134	131–138	94–169
Platelets, $\times 10^9$/L	81	136.0	120.7–151.2	29.0–347.0
Aspartate aminotransferase, U/L	74	117.2	95.6–138.8	16–451
Alanine aminotransferase, U/L	74	121.9	98.0–145.8	11–533
Alkaline phosphatase, U/L	51	236.1	191.5–280.8	57–606
Total bilirubin, μmol/L	49	29.1	19.3–38.0	5.1–135.1
γ-glutamyl transpeptidase, U/L	30	183.3	126.5–240.0	14–590
Lactic acid dehydrogenase, U/L	40	845.7	442.7–1,248.7	55–6,990
Serum creatinine, μmol/L	71	123.8	94.6–154.7	53.0–786.8
C-reactive protein, mg/L	73	875	645–1,104	5–2,700
Fever duration, days				
Before admission	73	6.5	5.1–7.6	0–30
After admission	71	4.5	3.5–5.3	0–21

evidence of cholelithiasis or obstructive jaundice. Persons with hyperbiliruwere often older, had higher serum levels of lactate dehydrogenase and C-reactive protein, and lower platelet counts than those without hyperbilirubinemia (Table 2).

Three cases of murine typhus also had serologic evidence of recent scrub typhus infections, and two cases had evidence for recent acute Q fever (Table 3). All five patients had at least a four-fold increase in IgG titers against *O. tsutsugamushi* or *C. burnetii*, in addition to *R. typhi*, in convalescent-phase serum samples. Clinically, these patients with co-infections were indistinguishable from those with murine typhus alone. All but one had recreational or occupational exposure to arthropods or animals. However, with appropriate therapy, all five patients responded well and recovered.

The febrile duration in patients before admission varied greatly, and on average they had fever for 6.3 days (Table 1). Sixty-one (75.3%) patients had fever for < 1 week, 15 (18.5%) for 8–14 days, and three (3.7%) for > 2 weeks. With appropriate antimicrobial therapy such as a tetracycline analog (doxycycline or minocycline) or a fluoroquinolone (levofloxacin, ciprofloxacin, or moxifloxacin), defervescence was noted within three days in 18 (42.9%) of 42 cases and within a week in 34 (81.0%) cases.

When we excluded 44 patients with frequent modifications of antimicrobial agents, 37 cases were included in efficacy analysis. Time to defervescence after the initialization of an appropriate drug (either a tetracycline analog or a fluoroquinolone), was significantly longer in 13 patients with

TABLE 2
Clinical characteristics of 49 patients with murine typhus with or without hyperbilirubinemia (serum total bilirubin ≥ 23.9 μmol/L) in southern Taiwan, 1992–2009*

Characteristic	No. positive/no. tested (%) or mean ± SD (no. cases with data)		*P*
	With hyperbilirubinemia (n = 17)	Without hyperbilirubinemia (n = 32)	
Male sex	12/17 (70.6)	23/32 (71.9)	0.924
Prolongation of activated partial thromboplastin time	11/15 (73.3)	13/21 (61.9)	0.473
Prolongation of prothrombin time	4/15 (26.7)	5/20 (25)	1.0
AST/ALT > 1	11/17 (64.7)	15/27 (55.6)	0.548
Relative bradycardia	13/17 (76.5)	22/31 (71.0)	0.682
Surface antigen of hepatitis B virus	0/10 (0)	3/17 (10)	0.274
Hepatitis C virus antibodies	1/10 (10)	0/16 (0)	0.385
Age, years	59.9 ± 16.0 (17)	49.0 ± 19.9 (32)	0.045
Initial AST, U/L	177.5 ± 141.0 (17)	115.5 ± 68.2 (32)	0.169
Maximum AST, U/L	193.0 ± 181.5 (17)	116.9 ± 67.1 (32)	0.207
Initial ALT, U/L	179.8 ± 135.9 (17)	128.8 ± 100.3 (32)	0.294
Maximum ALT, U/L	180.6 ± 139.2 (17)	133.0 ± 103.2 (32)	0.378
Alkaline phosphatase, U/L	262.7 ± 151.9 (14)	237.9 ± 161.1 (24)	0.482
γ-glutamyl transpeptidase, U/L	241.9 ± 180.2 (12)	162.8 ± 134.1 (12)	0.128
Lactic acid dehydrogenase, U/L	862.3 ± 444.6 (8)	463.4 ± 296.4 (19)	0.011
Serum creatinine, μmol/L	106.1 ± 44.2 (17)	150.3 ± 185.6 (31)	0.829
Initial C-reactive protein, mg/L	1,206 ± 681 (16)	7,504 ± 5,802 (27)	0.025
Initial leukocyte count, $\times 10^9$/L	6.9 ± 3.6 (17)	8.0 ± 3.5 (32)	0.175
Initial hemoglobin level, g/L	137 ± 15 (17)	135 ± 20 (32)	0.809
Initial platelet count, $\times 10^9$/L	99.4 ± 48.4 (17)	144.9 ± 67.0 (32)	0.019
Fever before admission, days	6.9 ± 7.1 (17)	5.5 ± 5.3 (31)	0.609
Fever to effective therapy, days	6.8 ± 4.9 (15)	7 ± 6.25 (21)	0.948
Defervescence after effective therapy, days	6.1 ± 3.6 (16)	4.1 ± 3.3 (31)	0.015
Duration of hospitalization, days	10.8 ± 5.3 (17)	8.4 ± 5.5 (26)	0.042

* AST= aspartate aminotransferase; ALT= alanine aminotransferase.

TABLE 3
Clinical features of five patients with murine typhus and other rickettsial co-infections in southern Taiwan, 1992–2009*

Patient	Age, years/sex	Co-infection	Occupation/risk factor	Prodrome/rash/relative bradycardia	Initial leukocyte ($\times 10^9$/L)	Maximal total/direct bilirubin (μmol/L)	Maximal AST/ALT (U/L)	Antimicrobial therapy (days)	Febrile duration with therapy (days)
1	74/F	Scrub typhus	Residence in the mountainous area	Fever, chills, axillary lymphadenopathy/ no/no	7.14	11.9/–	56/52	Doxycycline (10)	1
2	68/M	Scrub typhus	Retired driver, mountain climbing	Fever, chills/rash over the abdomen/no	13.13	27.2/11.7	74/82	Doxycycline (14)	6
3	54/F	Scrub typhus	Leather worker, flea bite	Fever, chills, headache/ no /no	4.70	19.0/7.7	148/109	Doxycycline (11)	1
4	62/M	Acute Q fever	Farmer, duck breeding	Fever, headache/rash over neck/yes	4.99	6.8/1.7	76/60	Doxycycline (14)	5
5	54/M	Acute Q fever	Teacher	Fever, chills/no/no	11.30	–/–	100/150	Doxycycline (24)	5

* AST = aspartate aminotransferase; ALT = alanine aminotransferase. None of the patients had any complications and all recovered.

hyperbilirubinemia than in 24 patients without hyperbilirubinemia (6.1 versus 4.1 days; $P = 0.02$). The total duration of fever was 11.7 days in 31 patients treated with a tetracycline analog, similar to the 9 days in 6 patients treated with a fluoroquinolone ($P = 0.30$). Despite the duration of tetracycline therapy for those with hyperbilirubinemia being longer than that of those without hyperbilirubinemia (10.6 versus 6.5 days; $P = 0.02$), the period between initialization of tetracycline therapy to defervescence in patients with hyperbilirubinemia was similar to that of those without hyperbilirubinemia (5.1 versus 4.9 days; $P = 0.41$).

Five (6.2%) patients had a total duration of febrile illness of at least two weeks. Four (80%) were females, 3 (75%) of 4 with available serum data for total bilirubin had hyperbilirubinemia at initial presentation, and three (60%) had severe illness. Three of them had had fever for > 10 days before admission. One patient treated with oral minocycline therapy became afebrile within three days, and the other two patients became afebrile at five and eight days, respectively, after admission although no appropriate antimicrobial agents were given. Another two patients had fever for > 2 weeks even after being treated with ciprofloxacin or moxifloxacin for at least one week. One patient initially presenting with hyperbilirubinemia and fever for nine days responded poorly to one week of moxifloxacin treatment, and subsequently developed ARDS and died, resulting in an overall case-fatality rate of 1.2% (1 of 81).

Severe illness or organ dysfunction related to *R. typhi* infections, i.e., acute renal failure (6.2%, 5), aseptic meningitis (3.7%, 3), and ARDS (1.2%, 1), was uncommon. Patients with severe complications took longer to achieve defervescence with appropriate therapy (9 versus 4 days; $P = 0.025$), and also had a longer duration of hospitalization (11.6 versus 8.1 days; $P = 0.024$) than those without severe complications (Table 4). Four patients with initial serum creatinine levels > 221 μmol/L and a subsequent increase in the serum creatinine level by > 20% were regarded as having acute renal failure with peak levels of serum creatinine ranging from 238.7 to 998.9 μmol/L. However, none of the patients required emergent hemodialysis. Five patients with fever and headache received lumbar puncture examinations, and three underwent computed tomography of the brain. Three with abnormal CSF findings, but without erythrocytes in the CSF, were given a diagnosis of aseptic meningitis. Mild brain edema was noted in only one patient, and normal findings were noted in the other two patients. Mild pleocytosis (5 and 10 leukocytes/mm^3 with lymphocytic predominance, respectively) in two patients and increased protein levels in CSF (770 and 840 mg/L, respectively) in two patients were noted. One patient had mild hypoglycorrhachia (CSF/serum glucose level = 41.5%). All three patients became afebrile within 72 hours after admission and achieved complete recovery one month later.

DISCUSSION

In this study, the transmission of murine typhus was maintained throughout the year. However, most cases were diagnosed during the summer during May–October. It is possible that during this time persons spend more time on outdoor activities, and are subsequently at a higher risk of exposure to *R. typhi*. In addition, this finding is likely correlated with an

TABLE 4

Clinical characteristics of 81 cases of murine typhus with or without severe complications (i.e., acute respiratory distress syndrome, aseptic meningitis, or acute renal failure) in southern Taiwan, 1992–2009*

Characteristic	Severe complications		*P*
	Yes (n = 9)	No (n = 72)	
Age, year	52.8 ± 24.0 (9)	49.7 ± 17.3 (72)	0.558
Male sex	4/9 (44.4)	51/72 (70.8)	0.138
Prolongation of activated partial thromboplastin time	4/6 (66.6)	32/47 (68.1)	1
Prolongation of prothrombin time	1/6 (16.7)	15/45 (33.3)	0.651
Initial AST, U/L	100.9 ± 71.5 (7)	118.9 ± 95.3 (67)	0.775
Maximum AST, U/L	514.7 ± 1,063.5 (9)	138.3 ± 144.8 (71)	0.542
Initial ALT, U/L	167.3 ± 178.6 (7)	117.1 ± 92.9 (67)	0.698
Maximum ALT, U/L	342.9 ± 577.9 (9)	131.8 ± 113.6 (71)	0.568
AST/ALT > 1	3/7 (42.9)	32/52 (61.5)	0.427
Alkaline phosphatase, U/L	264.3 ± 205.0 (4)	233.8 ± 156.9 (7)	0.723
γ-glutamyl transpeptidase, U/L	127.0 ± 17.0 (2)	187.3 ± 156.6 (28)	0.966
Lactic acid dehydrogenase, U/L	2,743.2 ± 2,997.4 (5)	574.6 ± 399.1 (35)	0.066
Serum creatinine, μmol/L	238.7 ± 238.7 (8)	106.1 ± 97.2 (63)	0.034
Initial C-reactive protein, mg/L	642 ± 561 (9)	907 ± 1,028 (64)	0.290
Initial leukocyte count, $\times 10^9$/L	10.0 ± 6.2 (9)	7.4 ± 3.5 (72)	0.188
Initial hemoglobin level, g/L	131 ± 17 (9)	135 ± 17 (72)	0.272
Initial platelet count, $\times 10^9$/L	113.9 ± 69.6 (9)	138.7 ± 69.0 (72)	0.314
Relative bradycardia	5/6 (83.3)	43/65 (66.2)	0.656
Fever before admission, days	10.8 ± 10.1 (6)	5.9 ± 4.5 (67)	0.150
Fever to effective therapy, days	11.4 ± 10.8 (7)	6.3 ± 3.0 (49)	0.431
Duration of hospitalization, days	11.6 ± 3.0 (5)	8.1 ± 5.3 (59)	0.024
Defervescence after effective therapy, days	9.0 ± 5.7 (6)	4.0 ± 3.4 (67)	0.025
Total duration of fever, days	17.7 ± 9.6 (7)	9.9 ± 5.5 (70)	0.028

* Values are or mean ± SD (no. with data) or no. positive/no. tested (%). AST = aspartate aminotransferase; ALT = alanine aminotransferase.

increase in the flea population during the warmer months.[10] However, there are other possible determinants of seasonal variation of murine typhus, such as vector density in the field, rainfall, humidity, or recreational activities.

Patients with murine typhus in this study had an average age of 50 years of age, and most were males. The male-to-female ratio for patients with *R. typhi* infection has been reported to be 0.67–1.50 in previous studies,[1,8,20–22] but was 2.12 in our study. Such a sex discrepancy may be related to men having more opportunities to stay outdoors. Only one case was a pediatric patient in this series.

Similarly, among 345 patients with murine typhus in southern Texas, there were only five (1.45%) children.[1] Murine typhus in children has occasionally been reported.[21–23] The low incident rate is possibly related to less exposure to *R. typhi*, less clinical suspicion of murine typhus in children, or the lack of awareness of this disease among pediatricians. Another possible reason is that affected children would respond to azithromycin, which is a frequently used antibiotic in children in many countries to treat infections, especially of the respiratory tract. Therefore, unrecognized influenza-like symptoms may be treated easily.

Pulse-temperature dissociation, such as relative bradycardia, has been associated with bacterial (typhoid fever, Legionnaires' disease, leptospirosis, typhus, Rocky Mountain spotted fever, and Q fever), parasitic or viral infections, and non-infectious diseases.[24,25] Relative bradycardia was observed in 53% of 100 patients with scrub typhus in Thailand[24] and 73% of 60 patients with acute Q fever in southern Taiwan.[26] However, no relevant data have been reported for persons with murine typhus. Relative bradycardia was observed in 67.6% of the cases. Although the presence or absence of relative bradycardia is not specific, in febrile ambulatory persons, relative bradycardia, hepatomegaly, or increased serum aminotransferase levels have been independently associated with rickettsial infections, including murine typhus, in southern Taiwan.[27]

Acute hepatitis, the predominant clinical manifestation of murine typhus, has been reported in 73–92% of patients.[1,8–10,20,22] However, frank hepatitis with jaundice in murine typhus has rarely been reported, and only 3–11% of reported cases were associated with jaundice.[1,9,20] The definitions of acute hepatitis vary, making comparisons between reports difficult. Approximately two-thirds of our patients had biochemical hepatitis, and hyperbilirubinemia, defined as a total bilirubin level ≥ 1.4 mg/dL, was observed in 35.4% of our patients. The higher frequency of hyperbilirubinemia may be related to several factors. Hepatic involvement by *Rickettsia* spp. was not the sole explanation in our patients. Underlying hepatic disease such as viral hepatitis (approximately 10% with hepatitis B virus surface antigen and 5% with antibody against hepatitis C virus), fatty liver (50%), or co-infections (scrub typhus or acute Q fever), may contribute, at least partially, to hepatocellular or cholestatic injury.

It has been suggested that in patients with glucose-6-phosphate dehydrogenase deficiency, thalassemia, hemoglobin E disease, or murine typhus infection increases the risk of increased hemolysis.[9] This suggestion seems less likely to be the cause of a higher prevalence of hyperbilirubinemia in our patients because the prevalence of glucose-6-phosphate dehydrogenase deficiency and thalassemia in the general population of Taiwan is low, 2% and 1–3%, respectively.[28,29] Moreover, the predominant form of serum bilirubin in our patients with murine typhus was the direct form, which was different from the major increase of indirect bilirubin in the patient with hemolysis.

Murine typhus is often a self-limiting, influenza-like disease lasting for 1–3 weeks.[1,10] There have not been any reports of patients with murine typhus and fever for > 28 days. However,

6.2% of the 81 patients had fever for 19–35 days, and 2.5% (2 patients) had fever that persisted for more than two weeks despite administration of appropriate antimicrobial therapy. Thus, when there is delayed defervescence in febrile patients empirically treated with recommended agent(s), clinicians should not exclude the possibility of murine typhus, especially in patients with prolonged fever. In addition, such cases will probably require longer therapy, as has been reported in patients with acute Q fever.[26] The optimal therapeutic strategy for cases of murine typhus with delayed defervescence is unknown. Severe complications were noted in 1–4% of cases in southern Texas.[1] However, severe illnesses such as ARDS, aseptic meningitis, and acute renal failure, were present in 11.1% of our patients. This finding may be related to prolonged fever and hyperbilirubinemia.

The suggested antibiotic treatment for typhus group rickettsiosis is daily treatment of with 200 mg of doxycycline for 7–15 days,[30] and an alternative option is a three-day course of azithromycin.[31] Fluoroquinolones have been considered to be alternatives to tetracycline for Mediterranean spotted fever[30] and typhus group rickettsiosis.[32] Although there has been a case of murine typhus with poor clinical response to ciprofloxacin,[33] a retrospective comparative study involving 87 patients with murine typhus treated by monotherapy or combination therapy of ciprofloxacin, doxycycline, and chloramphenicol were regarded as showing similar therapeutic efficacy.[34] In the present study, six patients were treated with a fluoroquinolone, and their time to defervescence after antimicrobial therapy was similar to that for patients treated with tetracycline. However, the number of patients was too limited to draw any conclusions.

Rickettsia typhi can infect endothelial cells of small blood vessels, causing vasculitis at different levels, including renal glomeruli, and therefore leading to proteinuria.[35] Urinary abnormalities were found in 5 (18.5%) of 27 patients in one study.[12] However, one-fourth of our 40 patients had hematuria, and four had acute renal failure. To the best of our knowledge, there have been 13 cases of acute renal failure related to *R. typhi* infections since 1968.[8,10,11,19,36–39] These case-patients did no have renal failure or multiple organ dysfunction, and at least of them needed renal replacement therapy. Only one patient died of ARDS in our study. However, the long-term prognosis of patients with murine typhus and renal dysfunction remains obscure.

There were several limitations to this study. First, not all febrile patients without a definite diagnosis had complete serologic surveys for the cause of their febrile illness because not all acute-phase and convalescent-phase serum samples of these patients were available. Thus, the incidence and case numbers of murine typhus will be underestimated. Second, this is a retrospective study based on the review of medical records, and some of the medical information on the patients and laboratory data was missing. Third, documentation of relative bradycardia caused by the retrospective nature of the study, and the recent use of beta-blocker agents must be definitively excluded. Fourth, clinical diagnosis of patients with co-infections was based on serologic test results, and the likelihood of cross-reactivity of IgG/IgM responses between these pathogens must be considered. However, with a fourfold increase in IgG against *O. tsutsugamushi* or *C. burnetii*, in addition to *R. typhi* in convalescent-phase serum samples, patients with these characteristics cannot be definitively diagnosed as having simultaneous murine typhus and scrub typhus or Q fever infection, although they had had recent scrub typhus or Q fever infections.

In conclusion, cases of murine typhus were often found during the summer in southern Taiwan, and had acute febrile hepatitis. Those patients with hyperbilirubinemia tended to have a delayed recovery with antimicrobial therapy. Murine typhus should be added to the list of differential diagnoses for patients with fever, headache, relative bradycardia, increased serum aminotransferase levels, or proteinuria.

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Authors' addresses: Ko Chang, Department of Internal Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan; and Department of Internal Medicine, Kaohsiung Municipal Hsaio-Kang Hospital, Hsiao Kang District, Kaohsiung 812, Taiwan, E-mail: johnsonckk@yahoo.com.tw. Yen-Hsu Chen, Graduate Institute of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan; and Division of Infectious Diseases, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung 807, Taiwan, E-mail: d810070@cc.kmu.edu.tw. Nan-Yao Lee, Hsin-Chun Lee, Chia-Ming Chang, Chi-Jung Wu, and Wen-Chien Ko, Department of Internal Medicine, National Cheng Kung University Hospital, Tainan, Taiwan, E-mails: nanyao@mail.ncku.edu.tw, lhc0918@mail.ncku.edu.tw, cmchang@mail.ncku.edu.tw, wucj@nhri.org.tw, and winston@mail.ncku.edu.tw. Chun-Yu Lin, Division of Infectious Diseases, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung 807, Taiwan, E-mail: infectionman@gmail.com. Jih-Jin Tsai, Division of Infectious Diseases, Department of Internal Medicine, and College of Medicine, Faculty of Medicine, Kaohsiung Medical University, Kaohsiung 807, Taiwan; and Tropical Medicine Center, Kaohsiung Medical University Hospital, Kaohsiung 807, Taiwan, E-mail: jijits@cc.kmu.edu.tw. Po-Liang Lu, Tun-Chieh Chen, and Wei-Ru Lin, Division of Infectious Diseases, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung 807, Taiwan, E-mails: idpaul@gmail.com, idchen.tunchieh@gmail.com, and lwru@mail2000.com.tw. Hsiao-Chen Hsieh, Department of Internal Medicine, Kaohsiung Medical University, Medical College, Kaohsiung, Taiwan; and Department of Internal Medicine, Kaohsiung Municipal Hsaio-Kang Hospital, Hsiao Kang District, Kaohsiung 812, Taiwan, E-mail: cheetah.hsieh@msa.hinet.net. Ping-Chang Lai, Section of Infectious Diseases, Department of Internal Medicine, Tian-Sheng Memorial Hospital, No. 210, Section 1, Donggang Township, Pingtung County 928, Taiwan, E-mail: pclai.tw@msa.hinet.net. Chung-Hsu Lai, Section of Infectious Disease, Department of Internal Medicine, E-Da Hospital/I-Shou University, Jiau-Shu Tsuen, Yan-Chau Shiang, Kaohsiung 824, Taiwan, E-mail: laich6363@yahoo.com.tw.

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