ORIGINAL ARTICLE

Epidemiology of Acute Q Fever, Scrub Typhus, and Murine Typhus, and Identification of Their Clinical Characteristics Compared to Patients with Acute Febrile Illness in Southern Taiwan

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Background/Purpose: In Taiwan, acute Q fever, scrub typhus, and murine typhus (QSM diseases) are the most common rickettsioses, but their epidemiology and clinical characteristics have not been clarified. Diagnosis of these three diseases based on clinical manifestations is difficult, and most of their reported characteristics are identified by describing the predominant manifestations, without being compared with other diseases.

Methods: Serological tests for QSM diseases were examined simultaneously in patients suspected of the three diseases, regardless of which one was suspected. Clinical manifestations were recorded retrospectively from their charts. The characteristics of QSM diseases were identified by comparison with patients who had non-QSM diseases.

Results: From April 2004 to April 2007, a total of 226 cases of suspected QSM diseases were included. One hundred (44.2%) cases were serologically confirmed as QSM diseases (68 acute Q fever, 23 scrub typhus, and 9 murine typhus), and 126 (55.8%) cases were non-QSM diseases. Only 33 cases (33.0%) of QSM diseases were initially suspected at the time of hospital visit, whereas 54 cases (42.9%) of non-QSM diseases were incorrectly suspected as QSM diseases. Cases of Q fever and scrub typhus were distributed over plain and mountain areas, respectively. By multivariate analysis, relative bradycardia (OR [95% CI], 2.885 [1.3–6.4]; $p = 0.009$), radiographic hepatomegaly (OR [95% CI], 4.454 [1.6–12.3]; $p = 0.004$), and elevated serum aminotransferases (OR [95% CI], 5.218 [1.2–23.1]; $p = 0.029$) were independent characteristics for QSM diseases, and leukocytosis (OR [95% CI], 0.167 [0.052–0.534]; $p = 0.003$) was negative for the diagnosis of QSM diseases.

Conclusion: In southern Taiwan, acute Q fever is the most common rickettsiosis. QSM diseases should be suspected in febrile patients who present with relative bradycardia, hepatomegaly, and elevated serum aminotransferases, but without leukocytosis. [*J Formos Med Assoc* 2009;108(5):367–376]

Key Words: endemic flea-borne typhus, Q fever, rickettsia infections, scrub typhus, Taiwan

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Rickettsioses are common zoonoses in humans, which conventionally include diseases caused by *Rickettsia* spp., *Orientia tsutsugamushi* and *Coxiella burnetii* infections, although the latter two have been removed from the *Rickettsiales*.[1–3] The clinical manifestations of rickettsioses are usually nonspecific, including fever, chills, headache, myalgia, malaise, skin rash or eschar-like lesion, hepatomegaly, splenomegaly, thrombocytopenia, and elevated serum aminotransferases.[1–3] In addition to clinical manifestations, histories of field activity, traveling in an endemic area, and exposure to arthropod vectors and animal reservoirs usually provide hints for clinicians to diagnose rickettsioses. However, exposure history may be missed by patients because recalling of exact contact with infected vectors and animals can be difficult. Furthermore, inhalation of *C. burnetii* contaminated aerosols is the major transmission route of Q fever in humans, which makes a history of direct animal exposure not strictly necessary. Accordingly, it is difficult to diagnose rickettsioses based solely on epidemiological, clinical, and routine laboratory findings. Serological tests are the gold-standard for definitive diagnosis of rickettsioses, but they are not available universally in most hospitals, and are usually available in research laboratories only. Thus, further investigation of characteristics specific for rickettsioses is necessary for primary care physicians.

In Taiwan, Q fever (caused by *C. burnetii*),[4–8] scrub typhus (caused by *O. tsutsugamushi*),[9,10] and murine typhus (caused by *Rickettsia typhi*)[6,11] are the most commonly reported rickettsioses. However, the epidemiology of these three diseases has not been clarified and clinical clues in febrile patients are lacking in southern Taiwan. The clinical characteristics of Q fever,[2,7,8,12–14] scrub typhus,[3,15,16] and murine typhus[17–19] have been reported widely in the literature. However, most reports have just described the predominant manifestations of each disease, and not real characteristics identified by comparison with other diseases that may easily be misdiagnosed clinically as QSM diseases.

Thus, we conducted the current study to investigate comprehensively the epidemiology of acute Q fever, scrub typhus, and murine typhus (QSM diseases) in southern Taiwan, and attempt to identify their clinical characteristics by comparison with other diseases that can be misdiagnosed as QSM diseases.

Methods

Institution and patients

This study was conducted at E-Da Hospital, a regional hospital with 1100 beds that opened in Kaohsiung County in southern Taiwan in April 2004. The study was approved by the Institute Ethics Committee (E-MRP-096-035) and partially supported by a research grant of the E-Da Hospital (EDAH: 96-08). Patients clinically suspected as cases of QSM diseases were reported initially to the department of infection control of E-Da Hospital. Regardless of which disease was suspected clinically, all three QSM diseases were reported to the Center for Disease Control, Taipei, Taiwan (Taiwan CDC), and paired sera (acute and convalescent phase) were collected and sent to the contract laboratory of Taiwan CDC for confirmatory tests. For easier description, patients were divided into QSM diseases (acute Q fever, scrub typhus, or murine typhus) and non-QSM diseases (non-acute Q fever, scrub typhus, or murine typhus) according to the results of serological examinations. Patients aged < 18 years old, without paired sera for confirmatory tests, or without testing for all three diseases were excluded. The charts of the included cases were reviewed and the demographic data, clinical manifestations, results of laboratory and imaging examinations, and outcomes were recorded for retrospective analysis.

Definitions

An animal contact history indicated a recent history of direct contact with, keeping, or being close to animals, including domestic dogs, cats, pigs, sheep and cattle, and wild animals. Relative bradycardia was defined as a body temperature ≥ 38.9°C and heart rate < 110 bpm, without treatment with

calcium blockers, beta-blockers or antiarrhythmic agents. Radiographic hepatomegaly indicated hepatomegaly recorded in the formal reports of abdominal computed tomography (CT) or ultrasonography performed by radiologists or the gastroenterologists. Leukocytosis was defined as a white blood cell count > 10,000/mm³; anemia was defined as a hemoglobin level < 10 g/dL; and thrombocytopenia was defined as a platelet count < 150,000/mm³. "Initial diagnosis" was defined as the tentative diagnosis made by clinicians upon hospital visit or before the subsequent suspicion of QSM diseases. "Final diagnosis" was defined as that made after completion of serological tests for QSM diseases and other relevant examinations. The diagnostic rate of QSM diseases was the percentage calculated from the number of serologically confirmed cases divided by the number of suspected cases each month.

Confirmatory tests for QSM diseases

Serological tests for the presence of specific antibodies to *C. burnetii*, *O. tsutsugamushi* and *R. typhi* were performed by indirect immunofluorescence antibody assay in the contract laboratory of the Taiwan CDC, as previously described.[4,6,9] Acute Q fever was diagnosed by an anti-phase II antigen IgG titer of ≥ 1:320 and anti-phase II antigen IgM titer of ≥ 1:80 in a single serum sample, or a four-fold or greater increase of anti-phase II antigen IgG titer in paired sera. Scrub typhus was diagnosed by an antibody titer of IgM ≥ 1:80, or a four-fold or greater rise of total antibody (IgG + IgA + IgM) titer in paired sera for Karp, Kato and Gilliam strains of *O. tsutsugamushi*. Murine typhus was diagnosed by an antibody titer of IgM ≥ 1:80 or a four-fold or greater rise of titers of IgG against *R. typhi* in paired sera.

Confirmatory tests for hepatitis B virus (HBV) or hepatitis C virus (HCV) infection

The status of HBV and HCV infections was examined because, in Taiwan, they are endemic,[20] and elevated serum aminotransferases are common manifestation of QSM diseases.[6–8,21–23] HBV infection was defined as the presence of hepatitis B surface antigen in serum, detected by IMx® HBsAg (V2) assay (Abbott IMx® System; Abbott Diagnostics, Abbott Park, IL, USA). HCV infection was defined as the presence of antibody to HCV in serum, detected by IMx® HCV version 3.0 (Abbott IMx® System; Abbott Diagnostics).

Statistical analysis

The results were analyzed using a commercially available software package (SPSS version 12.0; SPSS Inc., Chicago, IL, USA). Categorical variables were analyzed using the χ^2 or Fisher's exact test as appropriate. Continuous variables were analyzed using Student's *t* test. Multivariate analysis was performed by logistic regression. All *p* values were two-tailed and $p < 0.05$ was considered statistically significant.

Results

Case identification

From April 15, 2004 to April 30, 2007, a total of 264 patients were suspected clinically as cases of QSM diseases at E-Da Hospital. Forty (15.2%) patients were excluded from the study, of whom, 21 (8.0%) were without paired sera for confirmatory tests, 11 (4.2%) were aged < 18 years old, and eight (3.0%) were without testing for all three diseases. Two patients were co-infected with acute Q fever and scrub typhus, and they were analyzed as different cases for each disease. Patients were divided into two groups for analysis: QSM diseases (serologically confirmed as acute Q fever, scrub typhus, or murine typhus) and non-QSM diseases (serological confirmed as non-acute Q fever, scrub typhus, or murine typhus). The study included 100 (44.2%) cases (98 patients) of QSM diseases (68 acute Q fever, 23 scrub typhus, and 9 murine typhus) and 126 (55.8%) cases of non-QSM diseases. In the cases of QSM diseases, only 33 (33%) had an initial diagnosis of QSM diseases upon hospital visit. In contrast, 54 (42.9%) cases of non-QSM diseases had been suspected as QSM diseases and were subsequently excluded by serological tests.

Resident and monthly distributions of QSM diseases

Figure 1 shows the resident distribution of cases of QSM diseases, which revealed that most cases of Q fever were distributed over northern Kaohsiung city and western Kaohsiung county; nearly half the cases of scrub typhus were distributed over eastern Kaohsiung county; and the cases of murine typhus were distributed sporadically. The monthly distribution of cases is shown in Figure 2. Cases of acute Q fever and scrub typhus were predominant from March to September and from June to October, respectively. The correct diagnostic rate of QSM diseases was higher from March to September.
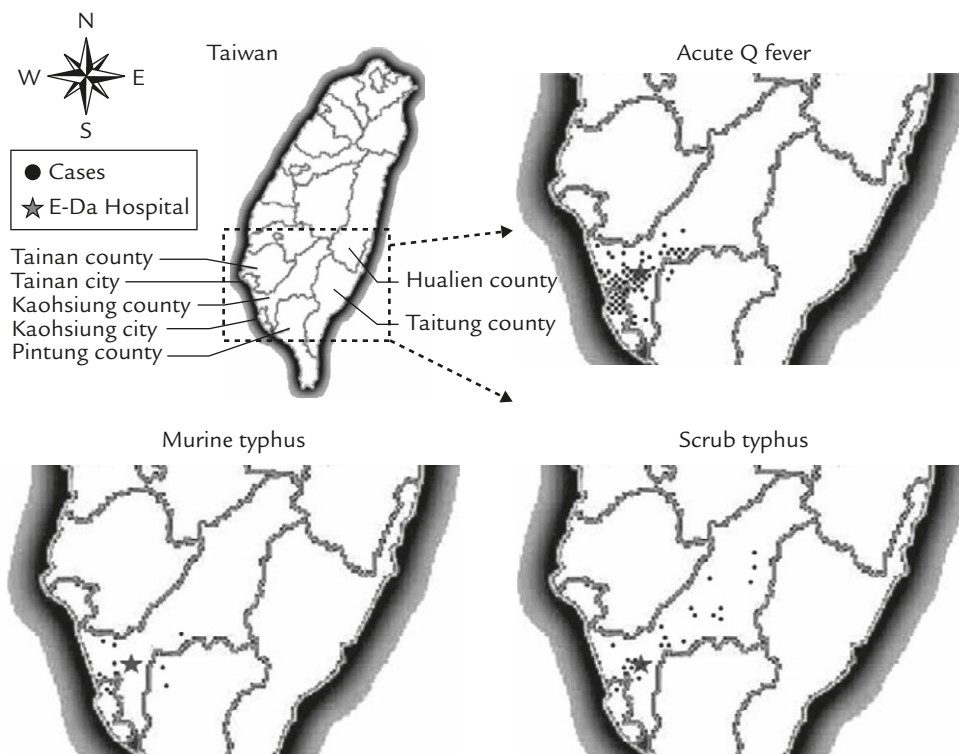

Figure 1. Resident distribution of cases of Q fever, scrub typhus, and murine typhus (QSM diseases) in southern Taiwan. *Right upper:* Most cases of Q fever were distributed over northern Kaohsiung city and western Kaohsiung county, a flatland area. *Right lower:* Nearly half the cases of scrub typhus were distributed over eastern Kaohsiung county, a mountainous area close to Taitung and Hualien counties. *Left lower:* The cases of murine typhus were distributed sporadically.
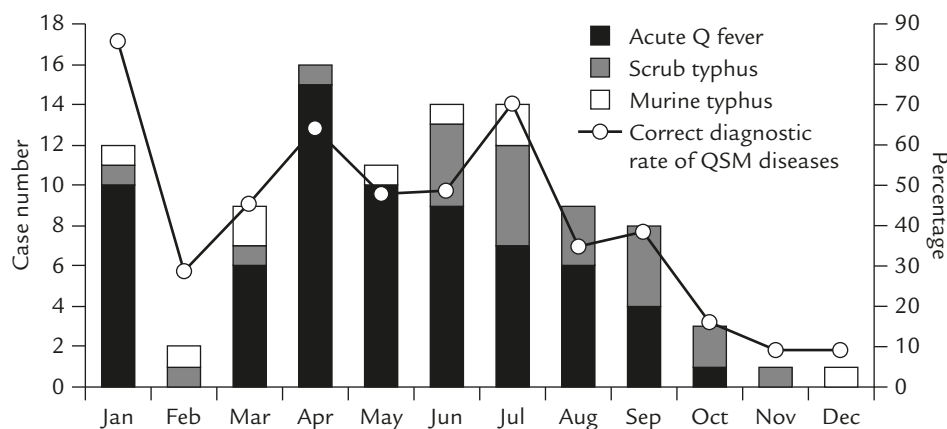

Figure 2. Monthly distribution of cases of Q fever, scrub typhus, and murine typhus (QSM diseases), and correct diagnostic rate of QSM diseases.

Identification of clinical characteristics of QSM diseases

The patients' demographic data and symptoms and signs are listed in Table 1. By univariate analysis, male sex (84.0% *vs.* 69.8%, *p* = 0.013), animal contact history (27.0% *vs.* 14.3%, *p* = 0.017), chills (73.0% *vs.* 56.3%, *p* = 0.01), headache (81.0% *vs.* 69%, *p* = 0.041), and relative bradycardia (49% *vs.* 25.4%, *p* < 0.001) were more common in cases of QSM than in non-QSM diseases. Arthralgia (2.0% *vs.* 11.9%, *p* = 0.005) and skin rash (16.0% *vs.* 30.2%, *p* = 0.013) were predominant in cases of non-QSM diseases. Table 2 shows the results of laboratory examinations and imaging studies. By univariate analysis, elevated liver enzymes (alanine aminotransferase [ALT] > 44 U/L, 94.9% *vs.* 66.7%, *p* < 0.001; and aspartate aminotransferase > 38 U/L, 97.0% *vs.* 70.3%, *p* < 0.001), and radiographic hepatomegaly (27.8% *vs.* 12.6%, *p* = 0.01) were more common in QSM diseases, and leukocytosis (6.0% *vs.* 28.6%, *p* < 0.001) was more common in non-QSM diseases. By multivariate analysis, relative bradycardia (OR = 2.885, 95% CI = 1.308–6.362, *p* = 0.009), radiographic hepatomegaly (OR = 4.454, 95% CI = 1.613–12.300, *p* = 0.004), and ALT > 44 U/L (OR = 5.218, 95% CI = 1.179–23.092, *p* = 0.029) were independent characteristics for QSM diseases, and leukocytosis (OR = 0.167, 95% CI = 0.052–0.534, *p* = 0.003) was for non-QSM diseases (Table 3).

Discussion

In the 100 cases of QSM diseases, acute Q fever (68, 68.0%) was the most common, followed by scrub typhus (23, 23.0%) and murine typhus (9, 9.0%). Similarly, in the 51 cases of rickettsioses reported by Lee et al, acute Q fever, scrub typhus, and murine typhus accounted for 28 (54.9%), 16 (31.4%), and seven (13.7%) cases, respectively.[6] Accordingly, acute Q fever rather than scrub typhus or murine typhus is the most common rickettsiosis in southern Taiwan. Only 33 (33.0%) cases of QSM diseases were initially suspected as QSM diseases upon hospital visit; in contrast,

54 (42.9%) cases of non-QSM diseases were initially suspected as QSM diseases. This indicates the difficulty in clinical diagnosis of QSM diseases.

Most of our cases were distributed in Kaohsiung county and city, which may have been because of the location of E-Da hospital (Figure 1). For cases of acute Q fever, most were distributed over northern Kaohsiung city and western Kaohsiung County, a plain area. This may have been because there are dairies in this region that contain many animal reservoirs of the causative pathogen, *C. burnetii*. For cases of scrub typhus, nearly half were distributed over eastern Kaohsiung County, a mountain area close to Taitung and Hualien counties. In Taiwan, the major distributions of cases of scrub typhus are eastern Taiwan (Taitung and Hualien counties, a mountain area) and an offshore island (Penghu and Kinmen counties).[9,10] This may explain the relatively greater number of cases of scrub typhus in eastern Kaohsiung county. Cases of murine typhus were distributed sporadically and the number of cases was relatively lower than for acute Q fever and scrub typhus. This may have been because of the improved sanitary conditions in Taiwan that have decreased the number of major reservoirs of *R. typhi*, rats and mice. For monthly distribution, cases of acute Q fever and scrub typhus were predominant from March to September and from June to October, respectively (Figure 2), and this is similar to previous studies.[4,5,9,10] However, the number of cases of murine typhus was so small that the predominant month was difficult to evaluate. The correct diagnostic rate of QSM diseases was higher from March to September, the spring and summer seasons in Taiwan. This may have resulted from the increased field activities of humans and increased activity of animal reservoirs in these seasons. However, the highest rate of correct diagnosis of QSM diseases occurred in January, and acute Q fever accounted for most of the cases of QSM diseases (10/12). This may have resulted from the increased thresholds of physicians attempting to examine QSM diseases during the non-prevalent season that subsequently increased the rate of correct diagnoses. The increased dairy production and delivery

Table 1. Demographic characteristics, symptoms, and signs of 226 cases of clinically suspected Q fever, scrub typhus, and murine typhus (QSM diseases)*

	QSM diseases (n = 100)	Non-QSM diseases (n = 126)	All (n = 226)	p[†]
Demographic characteristics				
Days from disease onset to hospital visit[†]	5.8 ± 2.9	5.3 ± 3.3	5.6 ± 3.1	0.226
Sex, M/F	84/16 (84.0/16.0)	88/38 (69.8/30.2)	172/54 (76.1/23.9)	0.013
Age (yr)	44.0 ± 13.5	44.4 ± 15.6	44.2 ± 14.7	0.835
Alcoholism	5 (5.0)	4 (3.2)	9 (4.0)	0.514
HBV or HCV infection[‡]	24/97 (24.7)	19/122 (15.6)	43 (19.6)	0.09
HBV	16/97 (16.5)	15/122 (12.3)	31 (14.2)	0.376
HCV	8/97 (8.2)	5/122 (4.1)	13 (5.9)	0.197
Liver cirrhosis[§]	1/90 (1.1)	1/95 (1.1)	2/185 (1.1)	1.0
Hypertension	13 (13.0)	16 (12.7)	29 (12.8)	0.946
Diabetes mellitus	7 (7.0)	9 (7.1)	16 (7.1)	0.967
CHF	1 (1.0)	1 (0.8)	2 (0.9)	1.0
COPD	2 (2.0)	2 (1.6)	4 (1.8)	1.0
Chronic renal insufficiency	0 (0)	2 (1.6)	2 (0.9)	0.504
Malignancy	1 (1.0)	3 (2.4)	4 (1.8)	0.632
Rural area travel history	30 (30)	33 (26.2)	63 (27.9)	0.526
Animal contact history	27 (27.0)	18 (14.3)	45 (19.9)	0.017
Symptoms				
Fever	98 (98.0)	118 (93.7)	216 (95.6)	0.114
Chills	73 (73.0)	71 (56.3)	144 (63.7)	0.01
Headache	81 (81.0)	87 (69.0)	168 (74.3)	0.041
Sore throat	11 (11.0)	24 (19.0)	35 (15.5)	0.097
Cough	35 (35.0)	41 (32.5)	76 (33.6)	0.697
Jaundice	5 (5.0)	6 (4.8)	11 (4.9)	0.934
Diarrhea	9 (9.0)	15 (11.9)	24 (10.6)	0.481
Abdominal pain/ discomfort	13 (13.0)	19 (15.1)	32 (14.2)	0.656
Nausea/vomiting	8 (8.0)	21 (16.7)	29 (12.8)	0.053
Arthralgia	2 (2.0)	15 (11.9)	17 (7.5)	0.005
Myalgia	26 (26.0)	35 (27.8)	61 (27.0)	0.765
General weakness	8 (8.0)	20 (15.9)	28 (12.4)	0.074
Signs				
Skin rash	16 (16.0)	38 (30.2)	54 (23.9)	0.013
Icteric sclera	4 (4.0)	7 (5.6)	11 (4.9)	0.759
Eschar	4 (4.0)	1 (0.8)	5 (2.2)	0.173
Lymphadenopathy	5 (5.0)	4 (3.2)	9 (4.0)	0.514
Hepatomegaly	3 (3.0)	0 (0)	3 (1.3)	0.085
Splenomegaly	1 (1.0)	0 (0)	1 (0.4)	0.442
Relative bradycardia[‖]	49 (49.0)	32 (25.4)	81 (35.8)	<0.001

*Data presented as mean ± standard deviation or n (%); [†]by univariate analysis between QSM and non-QSM diseases; [‡]confirmed by examinations of HBsAg and anti-HCV; [§]confirmed by abdominal ultrasonography or computed tomography; [‖]body temperature ≥ 38.9°C and heart rate < 110 bpm without medication with calcium blockers, beta-blockers, or antiarrhythmic agents. HBV = hepatitis B virus; HCV = hepatitis C virus; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease.

Table 2. Laboratory examinations and imaging findings of 226 cases of clinically suspected acute Q fever, scrub typhus, and murine typhus (QSM diseases)*

	QSM diseases (n = 100)	Non-QSM diseases (n = 126)	All (n = 226)	p[†]
Blood cell examination				
Days from disease onset to examinations	5.4 ± 2.8	4.9 ± 3.2	5.1 ± 3.0	0.211
Leukocytosis	6 (6.0)	36 (28.6)	42 (18.6)	< 0.001
Leukopenia	12 (12.0)	12 (9.5)	24 (10.6)	0.548
Lymphopenia	36 (36.0)	53 (42.1)	89 (39.4)	0.354
Monocytosis	9 (9.0)	20 (15.9)	29 (12.8)	0.125
Anemia	2 (2.0)	6 (4.8)	8 (3.5)	0.307
Thrombocytopenia	69 (69.0)	73 (57.9)	142 (62.8)	0.087
Biochemical examination				
Days from disease onset to examinations	5.8 ± 2.9	5.2 ± 3.2	5.5 ± 3.1	0.142
Creatinine > 2.0 mg/dL	3/92 (3.3)	10/112 (8.9)	13/204 (6.4)	0.099
ALT > 44 U/L	93/98 (94.9)	80/120 (66.7)	173/218 (79.4)	< 0.001
AST > 38 U/L	97/100 (97.0)	83/118 (70.3)	180/218 (82.6)	< 0.001
Total bilirubin > 1.3 mg/dL	11/33 (33.3)	16/43 (37.2)	27/76 (35.5)	0.726
CXR	96 (96.0)	117 (92.9)	213 (94.2)	0.314
Days from disease onset to CXR	5.8 ± 2.9	5.0 ± 3.2	5.4 ± 3.1	0.089
Pulmonary involvement on CXR	26/96 (27.1)	27/117 (23.1)	53/213 (24.9)	0.501
Unilateral infiltration	12/96 (12.5)	11/117 (9.4)	23/213 (10.8)	0.468
Bilateral infiltration	13/96 (13.5)	10/117 (8.5)	23/213 (10.8)	0.243
Consolidation	1/96 (1.0)	6/117 (5.1)	7/213 (3.3)	0.132
Abdominal ultrasonography or CT	90 (90.0)	95 (75.4)	185 (81.9)	0.005
Days from disease onset to abdominal ultrasonography or CT	7.1 ± 3.4	7.1 ± 3.7	7.1 ± 3.5	0.876
Cholecystitic change	19/90 (21.1)	15/95 (15.8)	34/185 (18.4)	0.350
Gallbladder wall thickening	15/90 (16.7)	14/95 (14.7)	29/185 (15.7)	0.718
Gallbladder distention	5/90 (5.6)	2/95 (2.1)	7/185 (3.8)	0.268
Hepatomegaly or splenomegaly	37/90 (41.1)	30/95 (31.6)	67/185 (36.2)	0.178
Hepatomegaly	25/90 (27.8)	12/95 (12.6)	37/185 (20.0)	0.010
Splenomegaly	25/90 (27.8)	23/95 (24.2)	48/185 (25.9)	0.58
Fatty liver	45/90 (50.0)	49/95 (51.6)	94/185 (50.8)	0.83
Cirrhotic change	1/90 (1.1)	1/95 (1.1)	2/185 (1.1)	1.0

*Data presented as mean ± standard deviation or n (%); [†]by univariate analysis between QSM and non-QSM diseases. Leukocytosis = white blood cell count > 10,000/mm³; leukopenia = white blood cell count < 4000/mm³; lymphopenia = lymphocyte count < 1000/mm³; monocytosis = monocyte count > 800/mm³; anemia = hemoglobin < 10 g/dL; thrombocytopenia = platelet count < 150,000/mm³; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CXR = chest X ray; CT = computed tomography.

Table 3.	Multivariate analysis of characteristics of Q fever, scrub typhus, and murine typhus	
Characteristics	OR (95% CI)	p
Relative bradycardia*	2.885 (1.308–6.362)	0.009
Radiographic hepatomegaly[†]	4.454 (1.613–12.300)	0.004
Leukocytosis[‡]	0.167 (0.052–0.534)	0.003
ALT > 44 U/L	5.218 (1.179–23.092)	0.029

Body temperature ≥ 38.9°C and heart rate < 110 bpm without medication with calcium blockers, beta-blockers, or antiarrhythmic agents; [†]hepatomegaly found by abdominal computed tomography or ultrasonography; [‡]white blood cell count > 10,000/mm³. OR = odds ratio; CI = confidence interval; ALT = alanine aminotransferase.

in winter in southern Taiwan may explain the high proportion of acute Q fever in January, but this hypothesis demands further investigation.

Relative bradycardia, radiographic hepatomegaly, and ALT > 44 U/L were independent characteristics for QSM diseases, and leukocytosis was negative for the diagnosis of QSM diseases (Table 3). Although relative bradycardia is known to be associated with several bacterial infections including typhoid fever, legionella pneumonia, chlamydial pneumonia, Q fever, scrub typhus, and Rocky mountain spotted fever,[24–26] its exact mechanism is not well understood. Ostergaard et al[26] demonstrated that relative bradycardia is a feature of typhoid fever, legionella pneumonia, and chlamydial pneumonia by comparison with other infectious diseases, and concluded that relative bradycardia occurs in diseases caused by intracellular Gram-negative bacteria. However, rickettsial disease was excluded from the control group in their study, which might limit the clinical application of their results for rickettsiosis when physicians encounter patients with relative bradycardia. Our results indicate that relative bradycardia is a common manifestation of QSM diseases (49.0%) in comparison with non-QSM diseases.

Elevated serum aminotransferases and radiographic hepatomegaly indicate liver involvement of QSM diseases. For Q fever, "doughnut" lesions, which present as granulomatous changes with fibrinoid rings and clear central spaces, are the pathological characteristics of Q fever with liver involvement[27–29] and 23–50% patients have hepatomegaly.[6–8,13,14,30,31] Pneumonia and hepatitis are the major clinical presentations of Q fever,[2] however, geographic differences exist, and hepatitis is the major presentation of Q fever in Taiwan.[6–8,21] For scrub typhus with liver involvement, granulomatous hepatitis has been reported as the pathological finding,[32] and about 30% of patients have an enlarged spleen and liver.[3] Although scrub typhus with abnormal liver function is rarely mentioned in Western literature, it is common in reports from Vietnam,[33] Japan[15] and Taiwan.[23,34] For murine typhus with liver involvement, pathological findings include sinusoidal infiltration and pseudo-granulomatous inflammation surrounding the necrotic hepatocytes.[35] Although elevated liver enzymes are found in 65–90% of cases of murine typhus,[17,19,35,36] hepatomegaly is rarely mentioned in the literature, with only 24% reported in one study in Thailand.[18] According to the results of previous studies and our study, liver involvement that presents as elevated liver enzymes and hepatomegaly is a characteristic of QSM diseases.

It is widely known that leukocytosis, particularly with "left shift", is a common finding in patients with bacterial infections. Leukocytosis is found in 1.5–30%,[2,6,8,13,14,30] 19%[15] and 20–30%[17,19] of cases of Q fever, scrub typhus and murine typhus, respectively. However, it has not been mentioned as a useful indicator to differentiate QSM from non-QSM diseases. This may be because most studies have described the predominant findings of QSM diseases without comparison with non-QSM diseases, which means that the relatively lower frequency of leukocytosis in the former will not have been detected. Leukocytosis is one of the hematopoietic changes of acute phase responses in inflammation and infection.[37] It results from recruitment of leukocytes (primary neutrophils) into the blood stream from bone marrow and from leukocytes adhered to the vascular endothelium. The circulating neutrophils subsequently migrate into the site of inflammation in response to chemoattractants or chemokines, a process known as chemotaxis.[38]

The intracellular survival of pathogens that cause QSM diseases may impair the function or reduce the degree of leukocyte recruitment, which results in less leukocytosis compared with infections caused by other pathogens, but this hypothesis demands further investigation.

It is unexpected that skin rash, a characteristic manifestation of rickettsioses, is not an independent characteristic for QSM diseases. Even more, we found that skin rash was significantly more common in non-QSM diseases, by univariate analysis (16.0% *vs.* 30.2%, $p = 0.013$) (Table 1). This may have been because Q fever, which rarely causes skin rash, accounted for 68% of QSM diseases in our study. However, skin rash was still not significantly predominant in scrub typhus/ murine typhus when compared with non-QSM diseases (34.5% *vs.* 30.2%, $p = 0.645$), after excluding cases of Q fever (data not shown). Another possible reason is that dengue fever, which usually causes skin rash, is also endemic in southern Taiwan, and it may have been included in non-QSM diseases. Our results indicated that the use of skin rash as a specific characteristic for QSM diseases may not be appropriate in southern Taiwan.

There are certain limitations in this study. Firstly, we tested only for QSM diseases. Other rickettsial diseases such as the spotted fever group, although never reported in Taiwan, were not investigated and they might have been included in the non-QSM diseases. Secondly, more than half ($n = 68$) and relatively few ($n = 9$) of the cases of QSM diseases were acute Q fever and murine typhus, respectively, which may limit the clinical application of the identified characteristics in other regions where the epidemiology of QSM diseases is different from that in southern Taiwan.

In summary, acute Q fever rather than scrub typhus or murine typhus is the most common rickettsiosis in southern Taiwan. It is difficult to diagnose rickettsioses by clinical manifestations only. The characteristics for QSM diseases identified in this study provide useful information to clinicians when they encounter patients suspected of these diseases, and allow clinicians to administer more confidently appropriate antimicrobial agents and request confirmatory tests.

Acknowledgments

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