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Prospective Study

Spectrum of cardiac manifestations and its relationship to outcomes in patients admitted with scrub typhus infection

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Abstract

AIM

To study the spectrum of cardiac manifestations in scrub typhus infection and assess its relationship to outcomes.

METHODS

Demographic data, electrocardiographic (ECG) changes, left ventricular (LV) systolic and diastolic function, myocardial injury (defined as troponin T > 14 pg/mL), and pericardial effusion were documented. Myocarditis was diagnosed when myocardial injury was associated with global LV systolic dysfunction. The relationship between myocarditis and outcomes was assessed using logistic regression analysis and expressed as odds ratio (OR) with 95%CI.

RESULTS

The cohort ($n = 81$; 35 males) aged 49.4 ± 16.1 years (mean, SD) presented 8.1 ± 3.1 d after symptom onset. The APACHE-II score was 15.7 ± 7.0 . Forty-eight (59%) patients were ventilated, and 46 (56%) required vasoactive agents. Mortality was 9.9%. ECG changes were non-specific; sinus tachycardia was the most common finding. Myocardial injury was evident in 61.7% of patients and LV systolic dysfunction in 30.9%. A diagnosis of myocarditis was made in 12.3%. In addition, seven patients with regional wall motion abnormalities had LV systolic dysfunction and elevated cardiac enzymes. Mild diastolic dysfunction was observed in 18 (22%) patients. Mild to moderate pericardial effusion was seen in 51%. On multivariate logistic regression analysis, patients with myocarditis tended to be older (OR = 1.04, 95%CI: 0.99-1.09), had shorter symptom duration (OR = 0.69, 95%CI: 0.49-0.98), and tended to stay longer in hospital (OR = 1.17, 95%CI: 0.98-1.40). Myocarditis was not associated with increased mortality.

CONCLUSION

In scrub typhus infection, cardiac manifestations are frequent and associated with increased morbidity but not mortality.

Key words: Scrub typhus; Myocarditis; Outcome

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Core tip: This study characterizes the cardiac manifestations in scrub typhus using a combination of clinical parameters, biomarkers, and echocardiography. In this prospective cohort study, 81 patients admitted with scrub typhus infection were enrolled. A wide range of cardiac manifestations were observed from non-specific electrocardiographic changes to pericarditis, myocarditis, and circulatory shock. Myocarditis occurred in 12.3% of the patients. Patients with myocarditis had significantly shorter symptom duration (OR = 0.69, 95%CI: 0.49-0.98) and tended to stay longer in hospital (OR = 1.17, 95%CI 0.98-1.40). An effect on mortality was not demonstrable.

Karthik G, Sudarsan TI, Peter JV, Sudarsanam T, Varghese GM, Kundavaram P, Sathyendra S, Iyyadurai R, Pichamuthu K. Spectrum of cardiac manifestations and its relationship to outcomes in patients admitted with scrub typhus infection. *World J Crit Care Med* 2018; 7(1): 16-23 Available from: URL: <http://www.wjgnet.com/2220-3141/full/v7/i1/16.htm> DOI: <http://dx.doi.org/10.5492/wjccm.v7.i1.16>

INTRODUCTION

Scrub typhus, caused by *Orientia tsutsugamushi*, is endemic in the "tsutsugamushi triangle". It accounts for nearly 50% of the cases of acute, undifferentiated

febrile illness in some settings^[1], and is associated with significant morbidity. Although the overall case fatality rate of patients admitted with scrub typhus infection is reported to be 9%^[2], in those presenting with severe illness and requiring intensive care unit (ICU) admission, mortality may be as high as 24%^[3]. There are reports that scrub typhus can cause myocarditis and myocardial dysfunction^[4-7]. However, the magnitude of this problem and its impact on outcome are unclear.

Myocarditis is postulated to occur as a result of disseminated endothelial infection of the small vessels or secondary immune mediated mononuclear inflammation^[5]. In a study of 31 patients who died of scrub typhus infection during World War II, post-mortem findings showed varying degrees of myocardial inflammation in 25 cases^[6]. In a recent study of 35 children with scrub typhus infection^[5], myocarditis with cardiogenic shock was reported in 34%. In a systematic review of 76 articles on scrub typhus involving 19644 patients, only four studies reported data on myocarditis^[8]. Pooled analysis of these four studies^[8] suggested a strong association between myocarditis and mortality (24% vs 4%; $P < 0.001$). There is a paucity of prospective studies that have systematically characterized cardiac manifestations in scrub typhus. This study detailed the spectrum of cardiac manifestations in scrub typhus infection and assessed its relationship to outcomes.

MATERIALS AND METHODS

Patients and setting

Adult patients admitted with an acute febrile illness (AFI) between June 2012 and January 2014 to the medical ward, medical ICU, or high dependency unit (HDU) of a tertiary care teaching hospital in India were considered for inclusion. Since a majority of patients with scrub typhus infection manifest thrombocytopenia, only patients with AFI and thrombocytopenia (platelet count $< 150000/\text{cmm}$) were screened. This was done because the study protocol required an echocardiographic assessment within 48 h of admission as well as additional serological tests. Given that the serological tests are batched for analysis and are not done daily, and since the institution handles a large number of patients with AFI, the additional screening criteria ensured that patients with a low probability of scrub typhus infection were not subject to additional tests and echocardiographic evaluation.

A diagnosis of scrub typhus was made when a patient with an AFI had a positive IgM enzyme-linked immunosorbent assay (ELISA) for scrub typhus, with or without an eschar and other causes of fever were excluded^[5,8]. Patients with an alternative diagnosis and those unwilling to participate in the study were excluded.

Ethical approval and funding

The study was approved by the local Institutional Review

Board (No. 8104) and supported by an institutional research grant (Fluid Research Fund). Written informed consent was obtained from all the patients or from their next of kin if the patient was critically ill and unable to consent.

Diagnostic tests

All patients underwent routine tests that included complete blood count, liver function test, renal function test, electrolyte test, chest radiograph, and appropriate cultures and serological tests. Scrub Typhus detect IgM ELISA (InBios International Inc., Seattle, United States) was used for serological diagnosis. An optical density ≥ 0.5 was diagnostic of scrub typhus.

Cardiac enzymes, creatinine kinase muscle brain isoenzyme (CK-MB), and troponin T were determined for all the patients. CK-MB was measured using COBAS e411 from ROCHE diagnostics. The reference range for CK-MB in our laboratory is < 6.7 pg/mL for males and < 3.8 pg/mL for females. Troponin T was measured by electrochemiluminescence immunoassay using COBAS e-411 modular analytics (ROCHE). The reference range for troponin T is < 14 pg/mL. As troponin T is a sensitive marker of myocyte injury^[9], this test was used for screening and diagnosis of myocarditis; troponin T > 14 pg/mL was considered as evidence of myocardial injury.

All patients had an electrocardiogram (ECG) at recruitment; heart rate, ST-T changes, and rhythm abnormalities were documented. A transthoracic echocardiography was performed within 48 h of admission, using a Sonosite Micromax unit with a 1 to 5 MHz phased array transducer probe. Left ventricular (LV) systolic and diastolic function and presence of pericardial effusion were assessed. LV systolic function was assessed by ejection fraction (EF), cardiac index (CI), and stroke volume index (SVI). LV ejection fraction (LVEF) $< 50\%$ determined by M mode in the parasternal long axis view was considered as myocardial dysfunction. The CI and SVI were determined using the measured LV outflow diameter from the parasternal long-axis view and LV outflow tract velocity time integral in apical 5 chamber view. A diagnosis of myocarditis was made when global LV systolic dysfunction (LVEF $< 50\%$) was associated with cardiac enzyme elevation (Troponin T > 14 pg/mL).

LV diastolic dysfunction was assessed using the mitral inflow wave pattern measured on pulsed wave Doppler (PWD) ultrasound. The ratio between heights of early and late diastolic flow velocity peaks E and A was obtained. The early diastolic peak velocity of the medial mitral annulus was also measured by tissue Doppler imaging and designated as e' . Diastolic dysfunction was diagnosed when the E/A ratio was < 1 and / or E/e' was > 15 ^[10-12].

Shock was classified as cardiogenic, septic, or mixed, based on echocardiographic parameters, where measures of preload [central venous pressure (CVP) and inferior vena cava (IVC) variability], cardiac contractility (cardiac

index), and afterload [vascular resistance-systemic vascular resistance index (SVRI)] were used. Since CVP is not a reliable measure of preload^[13], non-invasive measurements of the IVC diameter and IVC variability (calculated by measuring the difference between the maximum and minimum diameters on the M-mode and dividing it by the mean of the two) were used for assessing preload. IVC variability was present when it was $> 18\%$ for ventilated patients with no spontaneous breaths and was $> 50\%$ in a spontaneously breathing patient. Patients with a low CI and high SVRI were categorized as having cardiogenic shock, while those with a high CI and low SVRI were categorized as the ones with septic shock. Patients with a clinical picture of septic shock but a low CI were considered with mixed shock.

Severity of illness

Severity of illness was assessed using the Acute Physiology and Chronic Health Evaluation II (APACHE-II) score^[14]. Organ dysfunction was evaluated using the Sequential Organ Failure Assessment (SOFA) score^[15]. Organ dysfunction was present when the organ specific SOFA score was ≥ 1 and organ failure when SOFA score was ≥ 3 ^[16].

Patient management and outcome parameters

All patients were managed with appropriate antibiotics and supportive therapy (hemodynamic support, ventilation, and renal replacement therapy) as indicated. In less sick patients, oral doxycycline was administered at 100 mg twice daily. In critically ill patients, particularly those in shock, intravenous azithromycin 500 mg once daily was used either alone or in combination with enteral doxycycline since intravenous doxycycline was not available at the time of study. In pregnant patients, only azithromycin was administered.

The primary outcome that was assessed was the incidence of myocarditis. Other outcomes that were evaluated included mortality, need for ventilation and dialysis, type of ventilatory support (invasive or non-invasive), and duration of ICU and hospital stay.

Validation

Three investigators (KP, TIS, and KG), trained in critical care sonology, did the echocardiographic assessments. Inter-observer variability validation studies were done at the start of the study on 20 randomly chosen patients. The agreement among the investigators was measured using kappa and interclass correlation co-efficient. The kappa for the categorical variable regional wall motion abnormality was 0.57, and the interclass correlation coefficients for non-categorical variables such as LVEF, E/a, left ventricular outflow tract (LVOT) diameter, IVC diameter, and E/e' were 0.76, 0.86, 0.87, 0.76, and 0.88, respectively. During the study, echocardiogram images of all the recruited patients were stored and reviewed by a certified sonologist (KP).

Table 1 Demographics, symptoms, co-morbidities, and laboratory parameters in patients with and without myocarditis

Characteristic	With myocarditis (<i>n</i> = 10)	No myocarditis (<i>n</i> = 71)	<i>P</i> value
Demographic			
Age, mean (SD), yr	56.5 (13.7)	48.4 (16.2)	0.14
Gender (female:male)	41:30:00	5:05	0.64
Illness duration, mean (SD), d	6.8 (3.1)	8.3 (3.0)	0.16
Symptom, <i>n</i> (%)			
Fever	10 (100)	71 (100)	1.00
Cough	2 (10)	27 (38)	0.27
Breathlessness	8 (80)	54 (76)	0.78
Altered mental status	3 (30)	12 (16.9)	0.32
Myalgia	5 (50)	25 (35.2)	0.36
Vomiting	3 (30)	19 (27.8)	0.83
Co-morbidity, <i>n</i> (%)			
Diabetes	0	16 (22.5)	0.09
Hypertension	1 (10)	14 (19.7)	0.46
Pregnancy	0	5 (7)	0.39
Coronary artery disease	0	2 (2.8)	0.59
Smoking	1 (10)	2 (2.8)	0.26
Laboratory parameter, mean (SD)			
Hemoglobin, g %	12.9 (3.6)	11.3 (2.2)	0.06
Total white cell count, cmm	11360 (5484)	10649.3 (4879)	0.67
Platelets, cmm	47400 (36039)	65376 (62668)	0.38
Creatinine, mg %	1.6 (1.1)	1.7 (1.5)	0.76
Total bilirubin, mg %	1.7 (1.1)	2.1 (2.0)	0.49
Direct bilirubin, mg %	1.3 (1.0)	1.6 (1.7)	0.55
Serum albumin, mg %	2.3 (0.7)	2.6 (0.5)	0.20
AST, U/L	173 (143)	142 (92)	0.37
ALT, U/L	69 (53)	71.7 (51)	0.88
Alkaline phosphatase, U/L	196 (105)	203 (108)	0.84
SOFA score	10.6 (2.8)	8.7 (4.0)	0.16
APACHE II score	17.1 (8.3)	15.5 (6.8)	0.50

n: Number of patients; SD: Standard deviation; AST: Serum aspartate aminotransferase; ALT: Serum alanine transaminase; SOFA: Sequential Organ Failure Assessment; APACHE: Acute Physiology and Chronic Health Evaluation; ICU: Intensive care unit.

Statistical analysis

Assuming an incidence of myocarditis in scrub typhus as 30%, with 10% precision, the sample size was calculated to be 84. Descriptive statistics were obtained for all variables in the study. Categorical and continuous variables were compared for outcome using the Fisher's exact test and Student's *t*-test, respectively. All continuous data are expressed as the mean with standard deviation (SD) unless the data are not normally distributed. A *P*-value < 0.05 was considered statistically significant. The presence of myocarditis was correlated with mortality and expressed as odds ratio (OR) with 95% confidence interval (CI). A bivariate logistic regression analysis was performed to identify factors associated with myocarditis. Clinically relevant factors with a *P*-value < 0.2 on bivariate logistic regression analysis were incorporated into a multivariate logistic regression analysis. Statistical analyses were done using SPSS version 15 and Stata 11 statistical package (Statacorp, College Station, Texas, United States).

RESULTS

Baseline characteristics

During the study period, 122 patients with suspected scrub typhus were screened for myocarditis; 103 patients were diagnosed with scrub typhus based on

presentation as AFI, a positive IgM ELISA for scrub typhus, and exclusion of other diagnoses. Nineteen patients were excluded due to poor echo window and three patients were excluded because they did not consent for the study. Therefore, the study cohort comprised of 81 patients (35 males) with a mean (\pm SD) age of 49.4 ± 16.1 years, who presented 8.1 ± 3.1 d after symptom onset. All patients presented with fever; dyspnea was present in 52 (76.5%) patients. Diabetes mellitus was the most common co-morbid condition (23.5%). Baseline characteristics are summarized in Table 1.

On examination, an eschar was present in 62 (77%) patients. Involvement of two or more organ systems was present in 79 (97.5%), and 7 (8.6%) had involvement of all six organ systems. Respiratory and cardiovascular system involvements were present in 90.1% and 62.9%, respectively. Forty-eight (59%) patients required mechanical ventilatory support and three (3.7%) patients required dialysis.

Cardiac parameters

Cardiac parameters are summarized in Table 2. Sinus tachycardia was the most common ECG finding (46.9%). Fourteen patients had two abnormal findings in the ECG and 18 (22.2%) had a normal ECG. Twenty-five (30.9%) patients had myocardial dysfunction, and 50

Table 2 Comparison of cardiac parameters in patients with and without myocarditis

Parameter	With myocarditis (n = 10)	No myocarditis (n = 71)	P value
Electrocardiography finding, n (%)			
Sinus tachycardia	3 (30)	35 (49.3)	0.25
ST-T changes	2 (20)	8 (11.3)	0.43
T wave inversion	3 (30)	5 (7)	0.023 ¹
QRS morphology changes	5 (50)	6 (8.5)	< 0.001 ¹
Supraventricular tachycardia	0	1 (1.4)	0.70
Atrial fibrillation	0	3 (4.2)	0.51
Wide QRS tachycardia	0	1 (1.4)	0.71
Sinus bradyarrhythmia	1 (10)	4 (5.6)	0.59
Cardiac biomarker, mean (SD)			
CK-MB (ng/mL)	14.1 (18.1)	5.9 (7.1)	0.009 ¹
Troponin T (pg/mL)	235.9 (475.2)	61.6 (136.5)	0.014 ¹
Echocardiography finding, mean (SD)			
LVEF	41.6 (8.8)	59.8 (13.3)	< 0.001 ¹
Cardiac index	2.7 (1.1)	2.6 (0.9)	0.79
Systemic vascular resistance	2417 (1280)	2354 (891)	0.85
E/A	0.9 (0.2)	1.2 (0.4)	0.06
E/e'	9.9 (4.0)	9.8 (3.4)	0.94
CVP, cm	13.5 (5.3)	10.9±5.2	0.15

¹Significant value. SD: Standard deviation; CK-MB: Creatinine kinase muscle brain iso-enzyme; LVEF: Left ventricular ejection fraction; E/A: The ratio between heights of early and late diastolic flow velocity peaks; E/e': The ratio between early mitral inflow velocity and mitral annular early diastolic velocity; CVP: Central venous pressure.

(61.7%) patients had myocardial injury. Myocarditis was diagnosed in ten (12.3%) patients. In addition, 12 patients had regional wall motion abnormality (RWMA) with seven patients manifesting myocardial injury and an LVEF of < 50%. Eighteen (22%) patients had evidence of diastolic dysfunction. Mild to moderate pericardial effusion was seen in 41 (51%) patients.

Sixty-seven patients had hypotension at recruitment; however, only 46 (56.8%) patients required vasoactive agents. In these 67 patients, echocardiographic parameters of cardiac index, SVRI and CVP calculated from IVC variability were used to categorize shock. In patients with myocarditis (n = 10), the clinical picture was cardiogenic shock in four patients, septic (vasoplegic) shock in two patients, and mixed shock in four patients. In the seven patients with RWMA with myocardial dysfunction, four had features of cardiogenic shock, two had features of septic shock, and one had mixed shock. Of the remaining patients, 22 had features of cardiogenic shock and six had features of septic shock while mixed type of shock was seen in 22.

Outcomes

Forty-nine (60.5%) patients required intensive care; 48 were mechanically ventilated. Thirty-nine patients required invasive ventilation, 15 required non-invasive ventilation, and seven were treated with both invasive and non-invasive ventilation. The mean (\pm SD) durations of ICU and hospital stay were 4.2 ± 4.4 and 9.2 ± 4.7 d, respectively. The overall hospital mortality, which included two patients discharged at request, was 9.9%. Myocarditis was associated with a significantly higher ($P = 0.024$) number of patients requiring vasoactive agents. The need and duration of ventilation, length of stay, and mortality were not significantly different

between those who developed myocarditis and those who did not (Table 3).

Factors associated with myocarditis

On bivariate logistic regression analysis (Table 4), patients with myocarditis tended to have shorter duration of symptoms prior to presentation to hospital ($P = 0.16$), higher organ dysfunction scores as assessed by SOFA ($P = 0.16$), and a longer stay in hospital ($P = 0.10$) when compared with those who did not develop myocarditis. Myocarditis was not associated with mortality ($P = 0.99$).

On multivariate logistic regression analysis incorporating age, duration of symptoms, SOFA score, and hospital length of stay, myocarditis was independently associated with shorter duration of symptoms (OR = 0.69, 95%CI: 0.49 to 0.98, $P = 0.04$). However, age and longer hospital stay only tended to be associated with myocarditis (Table 4). The "goodness of fit statistic" (Hosmer Lemeshow test, $P = 0.238$) was used to validate the regression analysis.

DISCUSSION

Scrub typhus is a common cause of AFI with multi-organ dysfunction in India. There is a paucity of literature on the spectrum of cardiac manifestations and its impact on outcome in scrub typhus. In this prospective study of 81 patients admitted with scrub typhus infection, cardiac manifestations ranged from non-specific ECG changes to pericarditis, myocarditis, and circulatory shock.

We observed, in our cohort, that ECG changes were non-specific. The most common ECG finding was sinus tachycardia (46.9%). Three patients had atrial fibrillation, while five had sinus bradycardia and one

Table 3 Outcomes in patients with and without myocarditis in scrub typhus infection

Characteristic	With myocarditis (n = 10)	No myocarditis (n = 71)	P value
Outcome variable, n (%)			
Needing ventilation	7 (70)	41 (57.7)	0.46
Non-invasive ventilation	3 (30)	12 (16.9)	0.32
Invasive ventilation	5 (50)	34 (47.9)	0.90
Duration of ICU stay, mean (SD), d	5.0 (4.8)	4.0 (4.4)	0.53
Length of hospital stay, mean (SD), d	11.6 (5.7)	8.9 (4.5)	0.10
Needing dialysis	1 (10)	2 (2.8)	0.26
Needing vasoactive agent	9 (90)	37 (52.1)	0.024 ¹
Mortality	1 (10)	7 (9.9)	0.99

¹Significant value. SD: Standard deviation; n: Number of patients; ICU: Intensive care unit.**Table 4 Bivariate and multivariate logistic regression analyses of factors associated with myocarditis in scrub typhus infection**

Variable	Bivariate analysis		Multivariate analysis	
	OR (95%CI)	P value	OR (95%CI)	P value
Age	1.03 (0.99-1.08)	0.14	1.04 (0.99-1.09)	0.08
Gender	0.73 (0.19-2.76)	0.64		
Symptom duration	0.84 (0.65-1.07)	0.16	0.69 (0.49-0.98)	0.04
APACHE-II score	1.03 (0.94-1.13)	0.49		
SOFA score	1.13 (0.95-1.34)	0.16	1.12 (0.89-1.41)	0.32
Need for ventilation	1.71 (0.41-7.15)	0.46		
Hospital length of stay	1.11 (0.98-1.27)	0.10	1.17 (0.98-1.40)	0.09
Mortality	1.02 (0.11-9.25)	0.99		

Variables with a *P*-value < 0.2 were incorporated into the multivariate logistic regression analysis; on multivariate logistic regression analysis, age and hospital length of stay tended to be associated with myocarditis while symptom duration was associated with myocarditis. Hosmer-Lemeshow goodness-of-fit test, *P* = 0.238. APACHE: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential organ failure assessment.

patient had a wide QRS tachycardia. ST-T and QRS morphology changes were observed in 12.3% and 13.6%, respectively. The ECG findings in our cohort are similar to the study by Watt *et al.*^[17], where findings were predominantly minor and non-specific.

Troponin T was used as the biomarker to indicate myocyte injury, since it is a more sensitive marker in patients clinically suspected to have myocarditis^[18]. Myocardial injury was diagnosed in 50 (61.7%) patients. Since troponin can be elevated in several conditions other than myocardial injury in critically ill patients^[19], the incidence of myocardial injury may have been overestimated in our cohort, particularly in patients with renal failure (*n* = 16). However, myocarditis was presumed only if myocardial injury coexisted with global myocardial dysfunction. Thus, it is unlikely that the prevalence of myocarditis in our study (12.3%) was affected by a possible overestimation of myocardial injury. It is also interesting to note that troponin T was elevated in 17 patients without any evidence of myocardial dysfunction or renal failure.

Echocardiogram is a key non-invasive tool in detecting impaired LV function in suspected myocarditis, even when subclinical^[7,18]. Depressed LVEF was observed in 25 (30.9%) patients. RWMA was seen in 12 patients, of whom seven had a LVEF of < 50%. Although the presence of new RWMA with myocardial injury would suggest myocardial infarction, it is possible that in this

clinical setting, it could also indicate focal myocarditis in these seven (8.6%) patients. However, this was not explored further.

LV diastolic dysfunction has not been previously described in scrub typhus. Eighteen patients had evidence of diastolic dysfunction; however, only two had *E/e'* > 15. Pericardial involvement has been reported in autopsy studies, case reports^[7,20], and case series^[21]. We observed mild to moderate pericardial effusion in 41 (51%) patients. However, none developed cardiac tamponade requiring intervention.

Forty-nine (60.5%) patients required intensive care admission. The proportion of patients presenting in shock in our study (56.8%) was higher than those of the earlier reports by Varghese *et al.*^[2] and Chrispal *et al.*^[1] (23.1% and 13.8%, respectively). This is likely due to selection bias of possibly excluding less sick patients, as outlined in the methods. However, it is interesting to note that the mortality in our cohort (9.9%) is similar to an earlier study (9%)^[2] and much lower than that of a study that included only critically ill patients (24.1%)^[3].

The frequency of occurrence of myocarditis in our adult cohort of patients with scrub typhus (12.4%) is lower than the 34% reported in the pediatric subset^[5]. The high frequency of occurrence in the pediatric study^[5] was attributed to the late presentation. In our study, myocarditis was associated with a trend to shorter duration of symptoms and higher SOFA score (Table 4). However,

APACHE-II score was not associated with myocarditis. There was no gender predilection to the development of myocarditis. On the other hand, there was a trend of increasing occurrence of myocarditis with increasing age. Myocarditis was not associated with an increased need for mechanical ventilatory support but tended to be associated with longer period of hospital stay. Further, myocarditis was not associated with increased mortality. On multivariate logistic regression analysis, myocarditis was associated with shorter duration of symptoms prior to presentation and prolonged hospitalization. Generally, myocarditis is thought to be a rare but serious complication of scrub typhus resulting in high mortality and presenting later^[1,2,8]. The shorter duration of symptoms in those with myocarditis in our study may indicate earlier presentation in those who develop more severe symptoms.

The lack of association between myocarditis and mortality in our study contradicts the observations of Taylor *et al.*^[8], who in a systematic review pooling data of four studies showed a significant association between myocarditis and mortality. The low mortality in our relatively small cohort ($n = 81$) may explain this difference. Further, as described in that review^[8], the diagnosis of myocarditis was made in the majority of studies based on clinical parameters and was not based on echocardiographic evaluation and cardiac enzyme elevation. This could have resulted in misclassification and a higher incidence of myocarditis. It is also likely that our study was not powered adequately to detect an association between myocarditis and mortality, since the sample size was calculated assuming an incidence of myocarditis of 30%. The smaller sample size also limited our ability to incorporate all clinical symptoms in the multivariate logistic regression analysis.

In scrub typhus infection, cardiac manifestations are frequent and are associated with increased morbidity but not mortality. Early recognition and focused management of cardiac complications may help reduce morbidity and mortality associated with scrub typhus infection. Histopathological studies may further clarify the understanding of the pathophysiology of cardiac manifestations in scrub typhus infection.

ARTICLE HIGHLIGHTS

Research background

Scrub typhus, a rickettsial infection caused by *Orientia tsutsugamushi*, is endemic in India, with mortality rates of up to 24% in critically ill cohorts. Although cardiac involvement has been described in scrub typhus infection, the literature is devoid of prospective studies on the nature and extent of cardiac involvement and its impact on outcomes. This study characterizes the cardiac manifestations in scrub typhus infection. Myocarditis was associated with shorter symptom duration but not with mortality.

Research motivation

Scrub typhus is endemic in the southern states of India, with a high case burden next only to malaria and dengue in the list of tropical infections. Disease occurrence is seasonal with peak during monsoons. It is associated with significant morbidity and mortality. Organ dysfunction is common and

necessitates intensive care admission. This subject being tropical was considered for study.

Research objectives

The primary objectives were to study the spectrum of cardiac manifestations in scrub typhus infection and to estimate the incidence of myocarditis. The authors planned to compare the outcomes in scrub typhus patients with and without myocarditis and further to identify the factors contributing to the occurrence of myocarditis. This would help understand the disease process better and enable more focused research and treatment.

Research methods

This was a prospective observational study where all patients suspected to have scrub typhus were considered. Those patients with proven scrub typhus were enrolled and clinical characteristics, cardiac biomarkers, and electrocardiographic and echocardiographic findings were noted. Standard definitions were used for the diagnosis of myocardial injury, left ventricular dysfunction, and myocarditis. Myocarditis was correlated with outcomes.

Research results

Myocardial injury was evident in 61.7% of patients and LV systolic dysfunction in 30.9%. A diagnosis of myocarditis was made in 12.3%. On multivariate logistic regression analysis, patients with myocarditis tended to be older (OR = 1.04, 95%CI: 0.99-1.09), had shorter symptom duration (OR = 0.69, 95%CI: 0.49-0.98), and tended to stay longer in hospital (OR = 1.17, 95%CI: 0.98-1.40). Myocarditis was not associated with increased mortality.

Research conclusions

In scrub typhus infection, cardiac manifestations are frequent and are associated with increased morbidity but not mortality.

Research perspectives

Myocarditis was diagnosed clinically in many of the previous reported studies. The use of biomarkers and echocardiography might improve the robustness of the definitions. Scrub typhus patients with myocarditis presented early to the hospital and tended to stay longer. Further insight into pathogenesis needs to be addressed by histopathological studies.

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