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Does the presence of an eschar correlate with severity of scrub typhus infection?

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ABSTRACT

Background & Materials and Methods: In scrub typhus (ST) the correlation of disease severity to the presence or absence of eschar is not known. We describe the differences between patients with an eschar and those without. **Results:** In the 193 patients, 105 (56%) had an eschar. Patients with an eschar had a higher incidence of renal failure (18.1% vs. 5.7%; P = 0.01), respiratory system involvement (30.5% vs. 13.6%; P = 0.01) and cardiovascular system (CVS) involvement (21.9% vs. 10.2%; P = 0.03). Involvement of the central nervous system, hematological system and gastro-intestinal tract were not statistically significant between the two groups. ST patients with an eschar had significantly higher requirement for noninvasive ventilation (9.1% vs. 1.9%; P = 0.04). Requirement of invasive ventilation and inotropic supports were the same in both groups. **Conclusion:** The presence of an eschar in patients with ST is associated with a higher incidence of renal dysfunction, CVS and respiratory system involvement and a greater requirement of noninvasive ventilatory support.

Key words: *Eschar, scrub typhus, severity*

INTRODUCTION

Scrub typhus (ST) is a zoonotic rickettsial disease endemic in many parts of Indian subcontinent. The causative agent, *Orientia tsutsugamushi,* a Gram-negative intracellular bacterium is inoculated into humans by the bite of an infected larva of trombiculid mites (*Leptotrombidium* species) while feeding on human skin, usually in warm, damp areas where pressure from clothing occurs. ST is characterized by disseminated immune mediated lympho-histiocytic vasculitic illness leading to multi-organ involvement. At the site of the chigger bite, a characteristic cutaneous lesion called "eschar" appears. The presence of eschar in a patient with ST varies widely from 9.5% to 86% of patients, as reported in various studies.[1,2] Earlier studies have shown the inoculum load of *O. tsutsugamushi* co-relates directly with the presence of an eschar, which could result in more severe disease. However, Kim *et al*. showed that patients with an eschar are probably indentified and treated earlier hence have a milder disease.[1] Hence this prospective study was undertaken to ascertain the differences in clinical features, degree of organ involvement and outcome among ST patients with an eschar and those without an eschar.

MATERIALS AND METHODS

This study was done in a 2700 bed university teaching hospital in South India, from October 2012 to February 2013. 193 consecutive adult patients who presented with an acute undifferentiated febrile illness and confirmed to have ST were included in the analysis. ST was confirmed in patients presenting with an acute febrile illness of <14 days duration and positive Scrub IgM ELISA (In Bios International, Inc., Seattle, USA) with other etiologies being negative.

Other infectious etiologies for acute febrile illness, like malaria, enteric fever, dengue fever and leptospirosis were ruled out by appropriate tests. The patients with ST were divided into two groups based on the presence or absence of eschar. Clinical features, organ involvement and outcome in both groups were compared.

The pathological involvement of organ system was defined as following:

- Hematological dysfunction:
  - Thrombocytopenia, or
  - Leucopenia/leukocytosis, or
  - Evidence of coagulopathy (deranged prothrombin time or activated partial prothrombin time).
- Respiratory dysfunction:
  - PaO_2/FiO_2 ratio <300, or
  - Need for ventilator support.
- Renal dysfunction:
  - Serum creatinine >2 mg/dL; or
  - Need for dialysis.
- Cardiovascular dysfunction:
  - Hypotension, or
  - Need for inotropic or vasopressor support.
- Hepatic dysfunction:
  - Serum bilirubin >2 mg/dL; or
  - >3-fold elevation of liver enzymes (serum glutamic oxaloacetic transaminase/serum glutamic-pyruvic transaminase); or
  - Elevated alkaline phosphatase.
- Neurologic dysfunction:
  - Alteration in the level of consciousness or
  - Neck stiffness with aseptic meningitis.

Statistical analysis was performed using SPSS version 16 (SPSS, Inc., Chicago, IL). Descriptive data are given as mean (standard deviation [SD]) or as median (range). Chi-square test or Fisher exact test was used to compare dichotomous variables and *t*-test or Mann–Whitney test was used for continuous variables as appropriate. The differences between the 2 groups were analyzed by univariate analysis and their 95% confidence intervals (CIs)

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were calculated. For all tests, a two-sided $P = 0.05$ or less was considered statistically significant.

This study was approved by the Institutional Review Board and patient confidentiality was maintained using unique identifiers.

RESULTS

A total of 193 patients were confirmed to have ST during the study period. The mean age of the patients was 39.5 years and there was a slight female predominance (56%). The majority of the patients were agricultural workers (40.4%) or housewives (39.9%). A pathognomonic eschar was present in 105 (56%) with common sites including the groin, genitalia, axilla, and chest.

The mean age among the ST patients with eschar was 45.4 (SD 14.5) years as compared to 37.2 (SD 13.7) years among the patients without an eschar (95% CI: 4.0-12.1, $P < 0.001$). Out of 105 ST patients with eschar, 52.4% were males whereas among those without eschar 67% were females ($P = 0.007$, odds ratio [OR] = 2.2; 95% CI: 1.2-4.0). An eschar was seen in 46.7% of agricultural workers [Table 1].

The mean duration of fever prior to presentation was 8.3 (SD 3.3) days in the eschar group and 7.9 (SD 2.6) days in the noneschar group ($P = 0.34$). Common symptoms in both the groups included fever, breathlessness, cough, nausea, vomiting, headache and myalgia. However, the complaint of dyspnoea was higher in ST patients with an eschar (38.1%) as compared to the patients without eschar (20.5%); ($P = 0.008$, OR = 2.9; 95% CI: 1.2-4.6). Patients without an eschar had a slightly higher incidence of headache (75% vs. 61.9%; $P = 0.05$, 95% CI: 0.3-1.0).

The total and differential white blood cell counts was similar both the groups. 14.4% of ST patients with eschar had severe thrombocytopenia (platelet count <20000 cells/cu mm) as compared to 18.2% patients without eschar ($P = 0.4$). Thus the presence of eschar was not significantly associated with any major hematological involvement or severe thrombocytopenia.

The mean total serum protein level among ST patients with an eschar was 7.0 (SD 0.8) g% while among those without eschar was 6.7 (SD 0.8) g% ($P = 0.04$; 95% CI: 0.05-0.48). The mean serum albumin level among ST patients with an eschar was 3.4 (SD 0.65) g% while among those without eschar was 3.0 (SD 0.60) g% ($P = 0.001$; 95% CI: 0.12-0.49). The mean serum glutamic oxaloacetic transaminase level among ST patients without eschar was 149.9 (SD 195.7) IU/ml which was significantly higher as compared to those with eschar was 98.8 (SD 98.9) IU/ml ($P = 0.02$; 95% CI: −7.9-94.1). The mean alkaline phosphate level among ST patients with an eschar was 136.6 (SD 104.7) IU/ml which was significantly higher as compared to those without eschar was 166.9 (SD 88.6) IU/ml ($P = 0.03$; 95% CI: −2.1-58.4). Total serum bilirubin value was >2 mg% among 11.5% patients of ST with eschar as compared to 19.5% ST patients without an eschar ($P = 0.12$). The clinical features and laboratory investigations are shown in Table 2.

Serum creatinine levels was elevated among ST patients without an eschar (1.6 (1.6 mg%) as compared to the ST patients with an eschar (1.3 (1.3 d to the ST patients with an eschar (1.3.3 tions ($P = 0.08$; 95% CI: 0.65-0.02).

Patients with an eschar had a higher incidence of renal failure (18.1% vs. 5.7%; $P = 0.01$), respiratory system involvement (30.5% vs. 13.6%; $P = 0.01$) and cardiovascular system (CVS) involvement (21.9% vs. 10.2%; $P = 0.03$). Involvement of the central nervous system (CNS) system, hematological system and gastro-intestinal tract were not statistically significant between the two groups [Table 3].

Scrub typhus patients with an eschar had a significantly higher requirement for noninvasive ventilation (9.1% vs. 1.9%; $P = 0.04$). Requirement of invasive ventilation and inotropic supports were the same in both the groups. During the study period there were only 2 deaths, one in each group [Table 4].

Table 1: Baseline characteristics

Characteristic	*Patients with eschar (n=105) (%)*	*Patients without eschar (n=88) (%)*	*P*
Age (years)	45.4±14.5	37.2±13.7	0.001
Gender			
Male	55 (52.4)	29 (33)	0.007
Female	50 (47.6)	59 (67)	
Occupation			
Agricultural workers	49 (46.7)	29 (32.9)	
Housewives	37 (35.2)	40 (45.5)	
Others	19 (18.1)	19 (21.6)	
Co-morbidities			
Diabetes mellitus	23 (21.9)	10 (11.4)	0.05
Hypertension	12 (11.4)	5 (5.7)	0.25
Ischemic heart disease	2 (1.9)	2 (2.3)	0.86
Chronic kidney disease	1 (1)	0 (0)	0.36
Chronic liver disease	0 (0)	1 (1.1)	0.27
Pregnancy	2 (1.9)	2 (2.3)	0.79

DISCUSSION

Scrub typhus affects almost a million people every year and mainly occurs in populations that encounter scrub vegetation as part of their occupation or daily life.[3,4] It is a clinically important disease because it is associated with many serious complications and has a mortality rate of 14-20%.[5-7] Its incidence in certain parts of India reaches endemic proportions and accounts for up to 50% of undifferentiated febrile illness in those areas during cooler months of the year.[3,7]

The clinical finding of a pathognomonic eschar in a patient with febrile illness is the most important clue to the diagnosis of ST. The eschar usually forms 7 days after inoculation, and is usually not noticed by the patients however, as the chigger bite is painless. The eschar incidence in our study was 56%, which is consistent with prior findings by Vivekanandan *et al.* who found an incidence of 46% but lesser than the 75.6% incidence reported by Inamdar *et al.* from hospitals near the same geographic location.[2,8] Sirisanthana *et al.* from Thailand and Kim *et al.* from Korea reported eschar incidences of 68% and 85.5% respectively.[1,9] This wide variation in incidence of an eschar may be explained by the different population groups, difference in skin color and also by the by the different strains of *O. tsutsugamushi* prevalent in each region.

Kim *et al.* has noted that the patients with an eschar may notice it and present earlier to a doctor in the course of the illness.[1] Appropriate antibiotics may be initiated earlier and this could have an impact on the outcome. However, in our study there was no difference in the mean duration of symptoms before presentation to

Table 2: Clinical features and laboratory investigations

Characteristic	*Patients with eschar (n=105)*	*Patients without eschar (n=88)*	*P*
Fever duration (days)	8.3±3.3	7.9±2.6	0.34
Chills	97 (92.4)	75 (85.2)	0.11
Myalgia	85 (81)	71 (80.7)	0.96
Headache	65 (61.9)	66 (75)	0.05
Vomiting	47 (44.8)	42 (47.7)	0.68
Abdominal pain	26 (24.8)	18 (20.5)	0.48
Breathlessness	40 (38.1)	18 (20.5)	0.008
Cough	19 (18.1)	16 (18.2)	0.98
Altered sensorium	8 (7.6)	3 (3.4)	0.21
Seizure	3 (2.9)	4 (4.5)	0.53
Overt bleeding	5 (4.8)	5 (5.7)	0.77
Laboratory investigations			
Hemoglobin (g%)	12.8±2.1	12.5±1.86	0.29
Total WBC (cells/cu mm)	10545±7057	9000±5333	0.18
Neutrophils (%)	69.6±14.9	63.2±16.7	0.09
Platelet count (cells/cu mm)	105116.19±93175	119781.61±72861	0.23
Platelets<20,000 cells/cu mm	15 (14.4)	16 (18.2)	0.48
Creatinine (mg%)	1.3±0.9	1.61±1.3	0.08
Urea (mg%)	38.6±36.0	48.7±46.7	0.13
CPK (U/L)	217.7±260.1	369.5±849.8	0.24
Bicarbonate (mmol/L)	19.9±3.9	19.4±4.4	0.43
Total bilirubin (mg%)	1.26±1.8	1.58±1.9	0.23
Bilirubin>2 mg%	12 (11.5)	17 (19.5)	0.12
Total protein (g%)	7.0±0.8	6.8±0.8	0.045
Albumin (g%)	3.4±0.7	3.1±0.6	0.001
SGOT (U/L)	98.8.8±98.9	149.9±195.7	0.021
SGPT (U/L)	74.5±80.2	94.3±111.9	0.156
ALP (U/L)	136.6±104.7	166.9±88.7	0.035

CPK=Creatine phosphokinase, SGOT=Serum glutamic oxaloacetic transaminase, SGPT=Serum glutamic-pyruvate transaminase, ALP=Alkaline phosphatase, WBC=White blood cell

Table 3: Organ involvement

Organ system	*Patients with eschar (n=105) (%)*	*Patients without eschar (n=88) (%)*	*P*	*OR*	*95% CI*
Hematological involvement	74 (70.5)	50 (57.5)	0.06	1.77	0.97 3.21
Renal involvement	19 (18.1)	5 (5.7)	0.01	3.67	1.31 10.28
CVS involvement	23 (21.9)	9 (10.2)	0.03	2.46	1.07 5.65
CNS involvement	8 (7.6)	3 (3.4)	0.21	2.34	0.6 9.09
Hepatic involvement	67 (63.8)	45 (51.1)	0.08	1.69	0.95 3
GI involvement	2 (1.9)	2 (2.3)	0.86	0.84	0.12 6.05
RS involvement	32 (30.5)	12 (13.6)	0.01	2.78	1.33 5.8

Hematological involvement: Thrombocytopenia (platelet count<100,000/cells cu mm), leucopenia (total WBC count<2500/cells cu mm), leucocytosis (total WBC count>11,000/cells cu cc) or evidence of coagulopathy; Renal involvement: Serum creatinine>2 mg/dL or need for dialysis; CVS involvement: Hypotension or need for inotropic or vasopressor support; CNS involvement: Alteration in the level of consciousness or aseptic meningitis; Hepatic involvement: Serum bilirubin>2 mg/dL or three fold elevation of SGOT/SGPT or elevated ALP; GI involvement: GI bleed; Respiratory involvement: PaO2/FiO2 ratio<300 or need for ventilator assistance. OR=Odds ratio, CI=Confidence interval, WBC=White blood cell, CVS=Cardiovascular system, CNS=Central nervous system, SGOT=Serum glutamic oxaloacetic transaminase, SGPT=Serum glutamic-pyruvate transaminase, ALP=Alkaline phosphatase, GI=Gastrointestinal, RS=Respiratory system

Table 4: Outcome

Supports and mortality	*Patients with eschar (n=105) (%)*	*Patients without eschar (n=88) (%)*	*P*
Invasive ventilation	10 (11.4)	6 (5.7)	0.16
Noninvasive ventilation	8 (9.1)	2 (1.9)	0.04
Inotropes	14 (13.3)	5 (5.7)	0.08
Dialysis	1 (11)	0 (0)	0.45
Death	1 (0.9)	1 (11)	

the hospital between patients with an eschar and those without. The location of eschars mostly in the flexural areas which can be easily over looked and dark skin of our population may make it difficult for the patients to notice and seek medical help. Health education of the people regarding the eschar and disease manifestation and modes of spread of disease is of paramount importance and can go a long way in early recognition of the disease.

In our study 78/190 (40.4%) of the patients were agricultural laborers and a similar percentage of patients were housewives (39.9%). This value is much higher than the 29% of the patients who were housewives in a study by Inamdar *et al*.[8]

Acute renal failure was significantly more among patients with an eschar (18.1%) as against 5.7% in those without an eschar. Other studies from India reported a 12-33% incidence of renal failure.[10,11] However they did not report any association between the presence of an eschar and incidence of renal failure. Pulmonary involvement in the form of acute lung injury was seen in 18.6% of all patients. Previous studies from India show an incidence of acute respiratory distress syndrome of 8-25% with majority of them requiring invasive ventilation.[7,12,13] Tsay and Chang reported no association between the presence of an eschar and pulmonary involvement.[13] In our study 8.2% of patients overall required invasive ventilation with no difference noticed between the two groups. However the requirement for noninvasive ventilatory support was significantly higher in patients with an eschar. CNS involvement is often a prominent clinical manifestation of ST infection and aseptic meningitis occurs in 12.5-26% of affected patients.[7,14,15] Some studies have shown altered sensorium to be an independent

predictor of mortality. In our study the presence of an eschar was not associated with a higher incidence of CNS involvement.

CONCLUSIONS

The presence of an eschar in patients with ST is associated with a higher incidence of renal dysfunction, CVS and respiratory system involvement and a greater requirement of noninvasive ventilatory support.

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