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Eschar is associated with poor prognosis in scrub typhus

Sir,

Scrub typhus occurs in almost all parts of India and is endemic[1]. Many researchers have reported the profile of scrub typhus from various parts of India with diagnosis based on IgM ELISA[2-4]. Eschar is pathognomonic for rickettsiosis including scrub typhus, but its presence has not been reported as a marker of disease severity. Kim *et al*[5] found absence of eschar to have prognostic significance in their study. We report here results of a retrospective analysis of IgM positive adult patients with scrub typhus showing eschar as a marker of severe rickettsiosis.

This retrospective, hospital record-based observational study was conducted in Dr Rajendra Prasad Government Medical College, Kangra, Tanda, Himachal Pradesh, India. The files of all fever patients from the record section who were admitted between January and December 2015, were reviewed. Those patients who had a diagnosis of scrub typhus based on confirmed IgM-positive ELISA test were included. The IgM kits used for testing were obtained from InBios International, Seattle, WA, USA. Those with co-infections such as malaria, leptospirosis, typhoid, tuberculosis and hepatitis, patients diagnosed as scrub typhus but IgM −ve and those diagnosed as scrub typhus on clinical suspicion where IgM ELISA was not done, were excluded. The data were extracted from the files and analyzed using SPSS software (version 23, SPSS, Inc., Chicago, IL, USA).

The patients were labelled as having sepsis, severe sepsis, septic shock and multi-organ dysfunction syndrome according to the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference Committee[6]. Patients were divided into two groups: eschar +ve and eschar −ve for analysis. Distribution of continuous variables in two groups, eschar +ve and eschar −ve, was compared using unpaired *t* test and Fisher's exact for categorical variables. Multivariate logistic regression was used to model the strength of association of other biologically plausible variables such as age and gender in addition to eschar on each of the outcome variables that were found to have significantly high distribution in patients with eschar.

Table I. Distribution of variables (clinical and biochemical) in scrub typhus patients (n=61)

Variable	n (%)
Males	19 (31)
Respiratory rate >24/min	22 (36)
Peripheral capillary SpO_2 <90%	24 (39)
Pulse rate >90/min	51 (84)
Mean blood pressure <70 mmHg	26 (43)
Renal involvement (oliguria/serum urea >60 mg/dl/serum creatinine >1.1 mg/dl)	32 (52)
Leucocyte count >12,000/µl or <4000/µl	34 (56)
Platelet count <80,000/µl	23 (38)
Rash	2 (4)
Eschar	22 (36)
Jaundice	17 (29)
Pain abdomen	30 (49)
Headache	27 (44)
Myalgia	49 (80)
Meningoencephalitis	6 (10)
Pleural effusion, ascites or pericardial effusion	2 (4)
Cholecystitis on ultrasound	27 (44)
Hepatomegaly on ultrasound	26 (43)
Inotrope support	15 (25)
Oxygen support	22 (36)
Steroid administration	8 (13)
Intravenous fluids	24 (39)
Death	7 (11)

SpO_2, oxygen saturation

A total of 74 records of fever with a diagnosis of scrub typhus were obtained, but only 61 patients had a documented IgM ELISA-positivity for scrub typhus. Since, no test was done to rule out leptospirosis in the first week of illness, all patients were given doxycycline (100 mg b.i.d) for 5-7 days and ceftriaxone injection (1g b.i.d) for 7-10 days to cover for both scrub typhus and leptospirosis. Scrub typhus was confirmed in these patients using IgM ELISA. No patient was found with co-infection of scrub typhus and leptospirosis. Malaria was ruled out in all patients using malaria rapid antigen card test.

Totally, 61 IgM+ scrub typhus patients were included, of whom 42 (69%) were females. Age range was 18-69 yr, with a mean of 41.19±13 yr. Mean hospital stay was 5.1±0.57 days. Mean fever duration before admission was 6.1 days, and mean temperature was 39.31°C. The distribution of clinical and biochemical variables in scrub typhus patients is shown in Table I. Among the symptoms, myalgia 49 (80%), pain abdomen 30 (49%), shortness of breath 28 (46%) and headache 27 (44%) were common. Jaundice 17 (28%), meningoencephalitis 6 (10%), rash 2 (3%), pleural effusion 1 (1.5%) and ascites 1 (1.5%) were other less common complaints.

Sepsis was established in 56 (92%), of whom 52 (85%) had severe sepsis. Mean blood pressure <70 mm Hg was present in 26 (42%) patients, and septic shock needing vasopressors was present in 15 (25%). Steroids were given to eight (13%), and supplemental oxygen was given to 22 (36%). Multi-organ dysfunction syndrome was diagnosed in 28 (46%). Ultrasound was suggestive of cholecystitis in 27 (44.26%) and that of hepatomegaly in 26 (43%).

Eschar +ve 22 (36%) patients were compared with eschar −ve 39 (64%) patients to see if the distribution of clinical, biochemical and outcome variables was different in these two groups (Table II). The baseline characteristics such as age and gender were comparable. Mean age in eschar +ve group was 42.5±14 yr, while it was 40.4±12 yr in the eschar −ve group. Multivariate logistic regression was used to model the strength of association of age, gender and eschar on each of the parameters that showed significantly high distribution in eschar +ve patients.

Table II. Strength of association of eschar with various clinical and biochemical parameters

Variable	Eschar +ve, n (%) 22 (36)	Eschar −ve, n (%) 39 (64)	Total	*P* value exact 2 sided
Respiratory rate >24/min	16 (72)	6 (15)	22	<0.001
TLC >12,000/µl or <4000/µl	12 (55)	22 (56)	34	0.1
Pulse >90/min	21 (95)	30 (77)	51	0.07
Mean blood pressure <70 mmHg	14 (64)	12 (31)	26	0.01
Oliguria or serum urea >60 mg/dl	17 (77)	12 (31)	29	0.001
Serum creatinine >1.1 mg/dl	14 (64)	9 (23)	23	0.003
SpO_2 <90%	17 (77)	7 (18)	24	<0.001
Platelets<80,000/µl	14 (64)	9 (23)	23	0.003
Bilirubin >2 mg/dl or AST/ALT >150 U/l	19 (86)	22 (56)	41	0.02
Ventilatory support	5 (23)	0	5	0.004
Death	6 (27)	1 (0.02)	7	0.007
Pain abdomen	15 (68)	15 (38)	30	0.03
Myalgia	21 (95)	28 (72)	49	0.04
Inotrope support	13 (59)	2 (0.05)	15	<0.001
Oxygen support	14 (64)	8 (20)	22	0.002
Steroid use	7 (32)	1 (2.5)	8	0.002
iv fluids	15 (68)	9 (23)	24	0.001
Cholecystitis on ultrasound	17 (77)	10 (26)	27	<0.001
Hepatomegaly on ultrasound	13 (59)	13 (33)	26	0.06

ALT, alanine transaminase; AST, aspartate aminotransferase; SpO_2, oxygen saturation; TLC, total leucocyte count; iv, intravenous

Keeping age and gender constant, eschar was found to have significant independent association with respiratory rate >24/min, mean blood pressure <70 mmHg, oliguria or serum urea >60 mg/dl, serum creatinine >1.1 mg/dl, oxygen saturation <90 per cent, platelet count <80,000/µl, bilirubin >2 mg/dl (or AST/ALT) >150 U/l, need for inotrope support, need for oxygen support, need for intravenous fluids, steroid use, pain abdomen, myalgia, findings of cholecystitis on ultrasound and duration of hospital stay (Table II).

Eschar is a common finding in scrub typhus and spotted fever group rickettsiosis, but its positive association with disease severity has not been established in clinical studies. Sonthayanon *et al*[7] from Thailand found presence of an eschar associated with higher bacterial load in blood, and they speculated that there might be a possible link between the development of an eschar and the size of initial inoculum or the virulence of the infecting strain. This study used molecular techniques for diagnosis and the association of eschar with high viral loads was a significant finding. We could not find any study showing positive association of eschar with the severity in disease in scrub typhus patients. Kim *et al*[5], however, showed the absence of eschar to be associated with severity, which was contrary to our observations. Sriwongpan *et al*[8] found almost equal (56±4%) distribution of eschar in non-severe, severe and deceased scrub typhus patients. On multivariate logistic regression using variables such as age, gender and eschar as predictors, significant independent association of eschar was found with the respiratory rate >24/min, mean blood pressure <70 mmHg, oliguria or serum urea >60 mg/dl, serum creatinine >1.1 mg/dl, oxygen saturation <90 per cent, platelet count <80,000/µl, bilirubin >2 mg/dl (or AST/ALT >150 U/l), need for inotrope support, need for oxygen support, need for intravenous fluids, pain abdomen, findings of cholecystitis on ultrasound and duration of hospital stay (Table III).

Eschar is produced as a part of immune response to the rickettsial antigens in the body and biopsy of the eschar shows leukocytoclastic vasculitis[7]. Hyperactive immune response behind eschar formation may also be responsible for renal, respiratory, haematological and circulatory organ involvement and severe illness

Table III. Multivariate logistic regression showing the strength of association of eschar with the variables

Variable	*P* value	Exp(B)	95 per cent CI for Exp(B)	
			Lower	Upper
Respiratory rate >24/min	0.0001	13.3	3.5	49.6
Leucocyte count >12,000/µl or <4000/µl	0.9	0.9	0.3	2.8
Pulse rate >90/min	0.1	5.3	0.6	46.8
Mean blood pressure <70 mmHg	0.02	3.8	1.2	11.9
Oliguria or serum urea >60 mg/dl	0.001	7.7	2.2	27.1
Serum creatinine >1.1 mg/dl	0.005	5.5	1.6	18.1
SpO_2 <90%	0.00006	14.3	3.8	53.2
Platelets <80,000/µl	0.004	5.7	1.7	18.5
Bilirubin >2 mg/dl or AST/ALT >150 U/l	0.03	4.6	1.1	19.0
Death	0.2	13.6	1.4	130.8
Jaundice	0.1	2.5	0.7	8.5
Pain abdomen	0.04	3.2	1.03	10.06
Myalgia	0.05	8.7	0.99	76.2
Need for inotrope support	0.0001	24.7	4.5	133.6
Need for steroid use	0.01	15.7	1.7	140.4
Need for oxygen support	0.003	6.1	1.8	20.3
Need for iv fluids	0.001	7.09	2.1	23.5
Cholecystitis on ultrasound	0.0004	10.1	2.7	37.2
Hepatomegaly on ultrasound	0.1	2.4	0.8	7.5

ALT, alanine transaminase; AST, aspartate aminotransferase; SpO_2, oxygen saturation; CI, confidence interval; iv, intravenous

in eschar +ve scrub typhus patients. Other plausible explanations include high inoculum load in patients with eschar leading to higher DNA loads and thus eschar and severe disease[7]. It may also be explained on the basis of virulence of the prevalent strains that causes eschar formation, higher DNA loads and severity of disease.

Our study had some limitations. The study was done in a tertiary care setting, so the results cannot be extrapolated to the scrub typhus patients in community. Arterial blood gas analysis (pO_2) was not done, so specific diagnosis of acute respiratory distress syndrome could not be made in the patients.

To conclude, the presence of eschar in IgM+ scrub typhus patients was found to be associated with symptom severity including renal, haematological, respiratory and circulatory systems, longer hospital stay and higher mortality in this group compared to eschar −ve IgM+ scrub typhus patients. Further studies need to be done to determine the causes behind this association.

***Conflicts of Interest*:** None.

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References

1. Rahi M, Gupte MD, Bhargava A, Varghese GM, Arora R. DHR-ICMR Guidelines for diagnosis & management of Rickettsial diseases in India. *Indian J Med Res* 2015; *141* : 417-22.
2. Koraluru M, Bairy I, Varma M, Vidyasagar S. Diagnostic validation of selected serological tests for detecting scrub typhus. *Microbiol Immunol* 2015; *59* : 371-4.
3. Sengupta M, Anandan S, Daniel D, Prakash JAJ. Scrub typhus seroprevalence in healthy Indian population. *J Clin Diagn Res* 2015; *9* : DM01-2.
4. Peter JV, Sudarsan TI, Prakash JAJ, Varghese GM. Severe scrub typhus infection: Clinical features, diagnostic challenges and management. *World J Crit Care Med* 2015; *4* : 244-50.
5. Kim DM, Kim SW, Choi SH, Yun NR. Clinical and laboratory findings associated with severe scrub typhus. *BMC Infect Dis* 2010; *10* : 108.
6. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med* 1992; *20* : 864-74.
7. Sonthayanon P, Chierakul W, Wuthiekanun V, Phimda K, Pukrittayakamee S, Day NP, *et al*. Association of high *Orientia tsutsugamushi* DNA loads with disease of greater severity in adults with scrub ty*phus*. *J Clin Microbiol* 2009; *47* : 430-4.
8. Sriwongpan P, Krittigamas P, Kantipong P, Kunyanone N, Patumanond J, Namwongprom S. Clinical indicators for severe prognosis of scrub typhus. *Risk Manag Healthc Policy* 2013; *6* : 43-9.