

## DISTRIBUTION OF ESCHARS ON THE BODY OF SCRUB TYPHUS PATIENTS: A PROSPECTIVE STUDY

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**Abstract.** Eschar is an important finding for the diagnosis of scrub typhus. The IFA test for possible scrub typhus was performed. The presence or absence of eschar was thoroughly examined. Among the 176 scrub typhus cases confirmed by IFA, 162 (92.0%) cases had eschar; 128 patients (79.5%) had eschars on the front of the body. Eschars were primarily detected in males within 30 cm below the umbilicus (19 patients, 35.8%). Distributions on the lower extremities and the front chest above the umbilicus were 22.6% (12 patients) and 20.8% (11 patients), respectively. A different pattern was seen in females. The most prevalent area was the front chest above the umbilicus, which accounted for 40.7% (44 patients) of all the detected eschars. Our study is the first report of a schematic diagram that shows the differences between the males and females with respect to eschar location in scrub typhus patients.

### INTRODUCTION

Scrub typhus is an acute febrile illness with the characteristics of high fever, headache, and rash. The disease is caused by the intracellular Gram-negative bacteria, *Orientia tsutsugamushi*, and is a major febrile disease that occurs in Korea, Japan, China, Thailand, and other south Asian countries during scrub typhus season.<sup>1</sup> The main reservoir of scrub typhus is wild rodents, and the vector for this disease is trombiculid mites.<sup>2</sup> Mites undergo four development stages: egg, larva, nymph, and adult. Morphogenesis from larva to nymph requires the mite to ingest animal tissue fluids. Infection of *O. tsutsugamushi* occurs when mites infected with *O. tsutsugamushi* bite humans and suck human tissue fluid. The site bitten by mites forms an eschar. The eschar is formed when the patient shows clinical symptoms such as fever, maculopapular rash, headache, anorexia, and lymph node enlargement.

Presence of eschar has been shown to be an important finding for diagnosis of rickettsialpox, scrub typhus, and other mite- or tick-borne rickettsiosis.<sup>3–5</sup> Because the eschar is where *O. tsutsugamushi* proliferates, as the site of inoculation of *O. tsutsugamushi* by mites, a large amount of *Orientia* should be present. The authors have reported that use of PCR with the eschar is helpful in making early diagnoses as well as in differentiating other eschar-like crusted lesions.<sup>6</sup> It is also very effective in identifying scrub typhus patients who were already treated with the antibiotics that have appropriate antimicrobial activity against *Rickettsia*.<sup>6,7</sup> Koss et al. reported that immunohistochemical staining using eschar showed 100% sensitivity for diagnosis of rickettsialpox.<sup>8</sup> Therefore, not only is eschar important for diagnosis of scrub typhus by presence of the eschar, it is also a vital sample for confirmation through immunohistochemical staining or PCR. Although eschars have high diagnostic value, the lesions are painless and without any itching sensation in most cases, causing the infection to be undetected by most patients. In addition, an

eschar is similar to a scab formed after trauma, and its size may be very small, which also hinders detection of eschar in many cases. Characterizing the preferential sites where eschars are formed may be very important for diagnosis of scrub typhus and some other rickettsioses. However, systematic studies on the preferential site of eschar formation, including differences in male and female bite victims, are rare. Therefore, we conducted a systematic study on the preferential sites of eschar formation in 176 definitely diagnosed patients who visited Chosun University hospital and its branches from September to December 2005.

### STUDY POPULATION AND METHODS

From September 1 to December 31, 2005, IFA testing for scrub typhus using serum was performed in adult patients older than age 18 years who visited Chosun University Hospital and its branches (Hae Nam Hospital, Jang Heung Hospital, and Cheon Dan Hospital), located in southwestern area of Korea, for diagnosis of acute febrile disease that developed within the prior 4 weeks. We selected adult patients who were suspected of having scrub typhus on the basis of either the determination of the clinicians or the history of fever together with eschar or a maculopapular skin rash. The sera of patients were assayed by previously described methods<sup>6,7,9,10</sup> for detecting the IgM and IgG antibodies against the standard *O. tsutsugamushi* antigen (Gilliam, Karp, Kato, and Boryong). The titer of positive serum was measured by 2-fold serial dilution, and the highest antibody value among the titers against the 4 serotypes was used as the antibody titer.

Definite diagnosis of scrub typhus was defined as in cases whose IgM titer against *O. tsutsugamushi* was  $\geq 1:80$  by IFA or whose IFA titer showed 4-fold or more increase in titer.<sup>11</sup>

Presence or absence of eschar on patients who participated in this study was thoroughly assessed. Confirmed areas of eschar are presented as a diagram (Figure 1). Patients who had  $\geq 2$  eschars were excluded from the comparison study of the preferential sites of eschar formation, and cases with a single eschar were drawn on the diagram. This study was conducted after obtaining the approval from the ethics committee of Chosun University Hospital.

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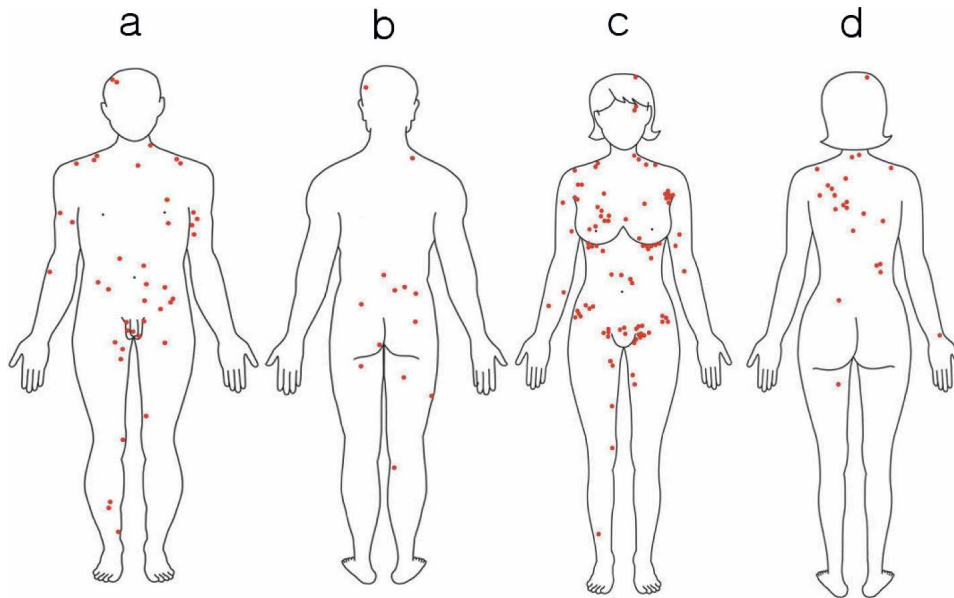


FIGURE 1. Sites that manifest an eschar in scrub typhus patients: (a) male front, (b) male back, (c) female front, (d) female back. This figure appears in color at [www.ajtmh.org](http://www.ajtmh.org).

Statistical analysis was done using  $\chi^2$  values to cross-analyze differences in eschar formation between sexes. A  $P$  value  $< 0.05$  was considered to be statistically significant. Data were analyzed by using SPSS version 12.0 software (SPSS Korea, Seoul, Korea).

## RESULTS

A total of 268 patients with possible scrub typhus visited Chosun University Hospital and its affiliated hospitals between September and December 2005. According to the results of indirect immunofluorescence assay, 176 patients were definitely diagnosed by having an IgM titer  $\geq 1:80$  or the IFA titer being increased 4-fold or more; 159 patients were confirmed by having an Ig M titer  $\geq 1:80$ , and 101 patients were confirmed by IFA titer rise 4-fold or more. Twenty-seven patients were confirmed to have other diseases. Sixty-five patients were not definitely confirmed with scrub typhus because a 4-fold increase in titer of antibody could not be proven due to insufficient follow-up.

Two patients were detected to have  $\geq 2$  eschars. One patient who had 2 eschars had an IgM level  $< 1:80$  at the time of visit, and follow-up observations could not be carried out; thus, the patient could not be definitely diagnosed as having scrub typhus. Another patient detected to have 3 eschars—one each on the face, chest, and abdomen—was excluded from the comparison study of the preferential site for eschar formation.

Among the 176 definitely diagnosed scrub typhus patients, 162 (92.04%) patients had eschars. Excluding the one patient who showed 3 eschars, the sites of the formation of eschar on 161 patients are drawn in Figure 1. Eschars formed preferentially on the front (79.5%) of the body in both sexes. Among the 53 males, 41 cases (77.4%) were confirmed to have eschar in the front area and 13 cases (22.6%) had eschar on the posterior area. For the 108 females, eschars formed on the front and back were seen in 87 cases (80.6%) and 21 cases

(19.4%), respectively. Cross-analysis using  $\chi^2$  values was performed to determine the presence of a difference in preferential site of eschar formation between sexes. The result showed a  $P$  value of 0.001 for the  $\chi^2$  value of 20.026, which signifies a noticeable difference in preferential eschar formation depending on sex (Table 1).

The primary regions of eschar formation in males were areas within 30 cm below the umbilicus (35.8%, or 19 cases), followed by the lower limbs (22.6%, or 12 cases), and the front chest above the umbilicus (20.8%, or 11 cases). However, the most prevalent development site in the females was the front chest above the umbilicus, which was different from the males: (40.7%, or 44 cases) of eschars were detected on the front anterior chest. In the area within 30 cm below the umbilicus, such as the inguinal area or the vicinity of the umbilicus, 24.1% (26 cases) of the eschars in females were found. A distinctive difference was seen in the distribution of the eschar between the sexes, with relatively more frequent appearance on the back area of the female (males, 1.9%;

TABLE 1

Comparison by sex for preferential eschar site on patients confirmed to have scrub typhus

Eschar location	Sex*	
	Male	Female
Head, face, and neck	3 (5.7%)	5 (4.6%)
Front chest above umbilicus (including the axilla)	11 (20.8%)	44 (40.7%)
Front and rear areas within 30 cm below the umbilicus (including the perineal, inguinal, and buttock areas)	19 (35.8%)	26 (24.1%)
Back	1 (1.9%)	17 (15.7%)
Upper extremities	7 (13.2%)	8 (7.4%)
Lower extremities	12 (22.6%)	8 (7.4%)
Total	52 (100%)	108 (100%)

\* There was a significant difference in the preferential site of eschar formation between sexes ( $P < 0.05$ ).

females, 15.7%) and less frequent appearance on the lower limbs of females (males, 22.6%; females, 7.4%).

## DISCUSSION

For scrub typhus patients, rickettsialpox patients and some other rickettsiosis patients, an eschar 5–20 mm in diameter is formed at the area bitten by mites or ticks. The area bitten by trombiculid mites initially forms a papule, which becomes a vesicle and then an ulcer, and which is finally covered by a black eschar. The vicinity of the eschar is surrounded by red erythema, and an eschar is typically formed at the time of the manifestation of symptoms.<sup>4</sup>

The typical eschar is found to be a slightly raised erythema surrounding a black necrotic center. However, for cases in which an eschar is formed in a warm and damp area, i.e., the axilla area or the perineum, a necrotic eschar is not formed; instead, an ulcer with a shallow, purulent base surrounded by a clear, erythematous band may be formed; in such cases, the eschar could possibly be improperly diagnosed and may be easily overlooked.<sup>12</sup>

For patients who perform outdoor activity and who visited the hospital for fever and rash, detection of eschar could be considered essential for the early diagnosis of some rickettsioses or scrub typhus. However, eschars do not cause pain or itching sensations in most cases. The eschars are generally small, and patients are usually not aware of actually being bitten by mites or even that an eschar is present in many cases.

Based on our experience, assessing the presence of lymph node enlargement could be applied as an important adjuvant method to find eschars. Eschars do not cause pain or itching sensations, but patients frequently feel lymph node swelling or tenderness in the draining lymph nodes; such tenderness and enlargement of lymph nodes could be of substantial help to detect eschars. In cases with enlarged neck lymph nodes or tenderness, there is a high possibility of having an eschar on the same side of the head and neck area; in cases with enlargement of the axillary lymph nodes, the possibility of detecting an eschar on the breast and upper limbs on the same side is high. The possibility of detecting an eschar on the perineum or lower limbs is high for the cases with enlargement of the inguinal lymph nodes. Therefore, for cases with enlarged or tender lymph nodes, a thorough physical examination of the body area that displays draining lymph nodes could be considered as prerequisite for detecting eschars.

The reported rate of eschar formation shows a substantial difference depending on investigators.<sup>13</sup> It has been reported that eschars could be detected relatively frequently on white-skinned Japanese children<sup>14,15</sup>; however, it is relatively difficult to detect eschars on dark-skinned Thai pediatric patients. In addition, it has been reported that for dark-skinned patients in whom early eschar lesion is atypical, the lesions could not be assessed as eschars and they could be easily overlooked.<sup>16</sup> However, these reasons are not sufficient for explaining the differences in reported eschar occurrence rates by the differences of population groups. Silpapojakul et al. reported in their retrospective study on dark-skinned Thai pediatric patients that eschar was detected in only 7%. However, eschars have been reported to be detected in 68% of the patients in a prospective study on Thai pediatric patients re-

ported by Sirisanthana et al.<sup>17</sup> In 2004, a study on scrub typhus patients residing in Jeollanam-Do Province (an area where 86.3% of the *O. tsutsugamushi* were the Boryong strain; unpublished data), in southwestern Korea, we have reported that the eschar occurrence rate was 85.5%. For patients residing in the Gang Won Province (an area where 13.3% of the *O. tsutsugamushi* is the Boryoung strain; unpublished data), in northeastern South Korea, however, the rate of manifesting eschar has been reported to be 46%.<sup>18</sup> Therefore, the reported differences in rates of eschars detected may not be due only to differences in population group and research designs but may be caused by the different strain of *O. tsutsugamushi* prevalent in each region.<sup>19</sup> Association of particular *Orientia* strains with the presence or absence of eschars would require further studies, including obtaining isolates from significant numbers of individual patients.

Among our enrolled 161 cases with a single eschar, 128 patients (79.5%) had eschars in the front of the body. James et al.<sup>20</sup> reported that mites do not seek their hosts actively but wait for the hosts to come into contact with them. Because of these characteristics, eschars might be formed in the front of the body. They also reported that clustered mite larvae are mostly seen on stalks, dried stems, and dead leaves rather than in the soil or on green blades of lalang grass. Mite activity tends to increase with rising temperature and lessens with decreasing humidity below the optimum limit.

Irons et al.<sup>12</sup> reported that the important factor contributing to eschar location is the warm, damp area where pressure from clothing occurs. After attachment, the mites bite the warm and damp areas where pressure is delivered, and then an eschar is formed.

In the study performed by Irons on U.S. army personnel stationed in Dutch New Guinea, it was reported that 45% of confirmed eschars were detected on the feet and legs. Perineum, inguinal area, and axilla are the preferentially eschar-manifested areas.<sup>12</sup> Nevertheless, this study could be considered as a study restricted to a special group, i.e., soldiers. In our report, among the confirmed patients, only one case was a soldier, and the rest of the cases were civilians; hence, the study could be considered to represent the sites where eschars are preferentially formed on a general population. In fact, most of the patients in this study were farmers, with a higher prevalence in females. In many of the studies reported in Korea, although the causality is not clear, scrub typhus developed preferentially in females rather than in males. In the diagram showing the sites of eschar formation (Figure 1), a distinct difference between males and females is shown. For females, pressure points from clothing are different from those of males. The lower part of the breast and its vicinity and the upper back are included. The distinct difference between the males and females is probably due to warmth and humidity formed by constrictive clothing, such as brassieres or tight underwear. The pressure caused by brassieres or tight underwear was thought to be a major factor generating such differences between males and females. Therefore, when patients suspected of having scrub typhus or rickettsiosis visit the hospital, the front chest, areas where the skin is folded, and areas within 30 cm below the umbilicus should be examined carefully in both sexes. It is also important to carefully examine the lower limbs of males and the front chest and back areas in females.

Our study has great clinical applications and determined

the preferential sites of eschar manifestation in scrub typhus patients, including the front and back sides of the body. It is also the first study to suggest a difference between the sexes; although it has not yet been reported, this report suggests the necessity of conducting systemic studies on the prevalent sites of eschar manifestation in rickettsialpox and other eschar-forming rickettsioses.

Delayed administration of effective antibiotics has caused fatal complications and death in several scrub typhus patients.<sup>14</sup> Therefore, rapid and accurate diagnosis is required for instituting the appropriate treatment of scrub typhus. For diseases manifesting eschar, such as scrub typhus, knowledge of the preferential areas where eschars form is very important for clinical diagnosis of scrub typhus and some other rickettsioses. If the preferentially manifested areas of eschar are well known, then early detection of the eschar of rickettsiosis and scrub typhus becomes easier. Physicians sometimes encounter eschar-like crust lesions in clinical practice. For cases in which eschar is not distinct, the early confirmation rate as scrub typhus eschar could be improved via PCR methods or immunohistochemical staining methods using eschar-like crust lesions.<sup>6</sup> This may contribute to reducing the mortality from scrub typhus or other rickettsioses.

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