Scrub typhus in children at a tertiary hospital in southern India: Clinical profile and complications

Manish Kumar, Sriram Krishnamurthy*, C.G. Delhikumar, Parameswaran Narayanan, Niranjan Biswal, Sadagopan Srinivasan

Department of Pediatrics, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Pondicherry, India

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KEYWORDS
Rickettsial infections; Scrub typhus; Myocarditis; Acute kidney injury; Children

Summary
Objective: To study the clinical profile of and complications in children with scrub typhus.
Design: Prospective observational study.
Setting: Tertiary care hospital.
Methods: Children up to 12 years of age who had a fever for more than five days without an identifiable infection were included. All children who were suspected of having rickettsial infections were defined as having scrub typhus if they had a positive Weil-Felix test result (OX-K 1:80 or more) and one or more of the following clinical features (after exclusion of other diagnoses): rash, edema, hepatosplenomegaly, lymphadenopathy, an eschar, and a tick bite or tick exposure.
Results: Thirty-five children were diagnosed with scrub typhus between February 2010 and February 2011. The age of the patients ranged from 1.5 to 12 years. Edema, crackles/rhonchi, hepatomegaly and hypotension were encountered in 60%, 23%, 91% and 34% of patients, respectively. An eschar was observed in 11% of the cases. Complications included myocarditis with cardiogenic shock in 34% of the cases and acute kidney injury in 20% of the cases. Anicteric hepatitis and thrombocytopenia were observed in 31% and 61% of cases, respectively. One patient died.
Conclusions: High incidences of myocarditis and acute kidney injury were observed, which indicates that the children were treated at a late stage of the disease. Clinicians should be cognizant that myocarditis and acute kidney injury are serious manifestations of pediatric scrub typhus.

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* Corresponding author at: Department of Pediatrics, JIPMER, Pondicherry 605006, India. Tel.: +91 413 2271040; fax: +91 413 2271040.
E-mail address: drsriramk@yahoo.com (S. Krishnamurthy).

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Introduction

Rickettsial infection, or rickettsiosis, is a zoonotic acute febrile illness caused by obligate intracellular, gram-negative bacteria from the genera *Rickettsia*, *Orientia*, *Ehrlichia*, *Neorickettsia*, and *Anaplasma*. Rickettsiosis is spread by tick or mite bites. Rickettsial infections are reported in various parts of the world [1–9]. Scrub typhus, which is caused by *Orientia tsutsugamushi*, is the most commonly reported rickettsial infection on the Indian subcontinent [3–6,10–12]. Rickettsial infections, including scrub typhus, are grossly under-diagnosed in India because of their non-specific clinical presentation, a limited awareness about the disease, a low index of suspicion among clinicians, and a lack of diagnostic facilities [10]. The majority of studies regarding rickettsial infections in India and other parts of the world are based on adult populations [1,7,10–13]. There is a paucity of studies regarding the incidence and clinical profile of scrub typhus in children from the Indian subcontinent [5,6,14–20], and the majority of published studies are retrospective studies [5,6,14,16,17] or sporadic case reports [18–20]. We conducted a prospective observational study at a tertiary hospital in Pondicherry, southern India, to study the clinical features and therapeutic outcomes of pediatric scrub typhus. The research objective was to determine whether the profile of children presenting with scrub typhus at our institution is different from that reported previously.

Materials and methods

The study was carried out in children up to age 12 years old who had a fever for more than 5 days without an identifiable infection. The patients were treated at a tertiary care hospital in Pondicherry between February 2010 and February 2011. The objective of the study was to determine the clinical profile of children admitted with scrub typhus.

Diagnosis of rickettsial infections

Rickettsial disease was suspected in patients who had a fever for more than 5 days without an identifiable infection and one or more of the following clinical features: rash, edema, hepatosplenomegaly, lymphadenopathy, an eschar, and a tick bite or tick exposure [14]. All children who were clinically suspected of having rickettsial infection because they had one or more of the above-mentioned features and who tested positive by the Weil-Felix test (OX-K 1:80 or more) were defined as having scrub typhus [10]. A favorable clinical response to doxycycline (defervescence within 48 h) was considered additional evidence of the disease [1–5].

Data collection

Clinical data, including the duration of the fever, associated symptoms, vital signs, and the general and systemic examination findings, were recorded. Patients were treated with a 10-day course of oral doxycycline (5 mg/kg/day BD). The response to treatment, the defervescence time, and the complications were noted. A careful search for eschars was performed for all patients. Data regarding age, sex, residential area, exposure to animals, exposure to farming and proximity to forest areas were collected.

Laboratory investigation

Other common infectious conditions that clinically mimic scrub typhus were ruled out by performing the following tests: a peripheral smear for the malaria parasite, a histidine rich protein II ELISA to diagnose malaria, a Widal test, a Dengue IgM antibody test, leptospira serology, a Paul–Bunnell test, urine and blood cultures, a tuberculosis test and an HIV-ELISA. Complete blood counts, erythrocyte sedimentation rate (ESR), chest X-rays, tests for renal and liver function, analysis of the urine for proteinuria, and serum electrolyte quantifications were performed at presentation for all cases and were repeated if necessary. Cerebrospinal fluid analysis was performed for selected cases with suspected meningitis. Serum creatine phosphokinase (CPK) levels, electrocardiography (ECG) and echocardiography were performed to look for evidence of myocarditis in cases complicated by congestive cardiac failure. The Weil-Felix (WF) test was performed for all of the cases. The WF Proteus agglutination assay (*P vulgaris*, OX-K strain agglutination) was performed on each sample by diluting the serum 1:20 to 1:1280. A WF titer of 1:80 (OX-K) or more was considered a positive result [10,14].

Definitions of complications in rickettsial disease

Myocarditis was diagnosed when the following conditions were observed: (i) congestive cardiac failure or cardiomegaly, (ii) hemodynamic compromise that required a vasopressor (>5 µg/kg/min of dobutamine or dopamine), (iii) left ventricular dysfunction identified by echocardiography without
Table 1 Clinico-epidemiological profile of children with scrub typhus.

<table>
<thead>
<tr>
<th>Demographic data</th>
<th>Signs and symptoms at presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Signs</td>
</tr>
<tr>
<td>Male</td>
<td>Fever</td>
</tr>
<tr>
<td>Female</td>
<td>&lt;7 days</td>
</tr>
<tr>
<td>Age in years</td>
<td>7–14 days</td>
</tr>
<tr>
<td>&lt;1</td>
<td>15–29 days</td>
</tr>
<tr>
<td>1–5</td>
<td>≥30 days</td>
</tr>
<tr>
<td>&gt;5–10</td>
<td>Headache</td>
</tr>
<tr>
<td>&gt;10–12</td>
<td>Myalgia</td>
</tr>
<tr>
<td>Habitat</td>
<td>Vomiting</td>
</tr>
<tr>
<td>Village</td>
<td>Cough</td>
</tr>
<tr>
<td>Town</td>
<td>Breathlessness</td>
</tr>
<tr>
<td>Forest</td>
<td>Abdominal pain</td>
</tr>
<tr>
<td>Sea-shore</td>
<td>Loose stools</td>
</tr>
<tr>
<td>Rice-field</td>
<td>Swellinga</td>
</tr>
<tr>
<td>Rodents</td>
<td>Bleeding manifestation</td>
</tr>
<tr>
<td>Dogs</td>
<td>Altered sensorium</td>
</tr>
<tr>
<td></td>
<td>Seizures</td>
</tr>
<tr>
<td></td>
<td>Oliguria</td>
</tr>
</tbody>
</table>

a Includes swelling over any part of the body (e.g. facial, leg or generalized swelling).
b There were no cases of jaundice.

previous cardiomyopathy and (iv) elevated CPK-MB levels in the blood, with or without ECG abnormalities. Hypotension was defined as a systolic blood pressure below the 5th percentile for the corresponding age, sex and height. Hepatitis was diagnosed when liver transaminases were found to be elevated (>40 U/L) [2]. Acute kidney injury (AKI) was diagnosed according to the Acute Kidney Injury Network (AKIN) definition and classification [21]. Acute respiratory distress syndrome (ARDS) was defined according to the American-European Consensus Conference on ARDS [22]. Thrombocytopenia was defined as a platelet count of less than 150,000/cu mm [3].

Results

Demographic data and clinical features

Thirty-five children were diagnosed with scrub typhus between February 2010 and February 2011. All cases were serologically confirmed. The age of the patients ranged from 1.5 to 12 years with a mean age of 6.3 years. Children between 5 and 10 years of age accounted for 60% of all cases. There were 20 males (57%) and 15 females (43%). The greatest number of cases was observed between the months of September and February. The majority of cases (31 cases) were from the neighboring districts of Villupuram (15 cases), Cuddalore (7 cases), Gingee (2 cases) and rural areas of Pondicherry (7 cases). Various environmental risk factors, such as tree cutting near the patient’s house, living close to a forest or playing around bushes and in rice-fields, were present in 34% of the patients. A history of exposure to rats or dogs was found for 61% of the patients.

The demographic data and clinical features at the time of presentation are shown in Table 1. All patients presented with fever, and the majority (60%) had a fever for 7–14 days prior to presentation. A cough, breathlessness and body swelling were found in 51%, 37% and 63% of the patients, respectively. Edema, crackles/rhonchi, hepatomegaly and hypotension were encountered in 60%, 23%, 91% and 34% of the patients, respectively. An eschar (Fig. 1) was observed in 11% of the patients (in the axilla or groin in 51% of

Figure 1 Photograph showing an eschar on the right thigh.
those cases), and splenomegaly was observed in 60% of the patients. Table 2 shows the complications observed among children diagnosed with scrub typhus. Myocarditis with cardiogenic shock at presentation was the most common complication (34% of the cases). Most cases of myocarditis (75%) occurred during the second week of illness. Acute kidney injury was noted in 20% of the cases, and 29% of these cases were in AKI stage 1, 42% were in stage 2, and 29% were in stage 3. A maculopapular rash was noted in 20% of the cases. A female child aged 4 years and 6 months developed left rectus palsy that resolved spontaneously within 5 days. Her CT brain scan was normal, and her lumbar puncture showed CSF pleocytosis. Anicteric hepatitis and a low platelet count (<150,000/cumm) were observed in 31% and 61% of cases, respectively.

### Laboratory parameters

The laboratory parameters of the cases are shown in Table 3. The total leukocyte count was elevated in 37% of the cases. An elevated serum creatinine level or a change in the serum creatinine level greater than 0.3 mg/dl, which is a diagnostic of AKI, was observed in 20% of cases. Hypoalbuminemia (serum albumin <3.0 g/dl) was found in 54% of the cases. The serum CPK level (total and MB fraction) was elevated in all cases with myocarditis. The Weil-Felix test was positive in all 35 cases (OX-K positivity). The majority of patients had titers of 1:320 or more. The cerebrospinal fluid of four patients was examined, and two of them had pleocytosis.

### Response to doxycycline

Most of the patients (34 out of 35 patients) responded dramatically to doxycycline. Doxycycline was used for 10 days. The duration of defervescence ranged from 18 h to 47 h. One patient, who had myocarditis, shock, AKI (requiring dialysis), hepatitis, encephalopathy and pericardial effusion, died.

### Discussion

In this study, we describe the profile of pediatric scrub typhus in a tertiary hospital in southern India. A positive Weil-Felix test with the OX-K strain of Proteus mirabilis is suggestive of scrub typhus, whereas a positive test with the OX 2 or OX 19 strains of Proteus suggests infection with typhus or the spotted fever group of organisms, respectively. There is a paucity of studies of children that detail the profile of scrub typhus on the Indian subcontinent during the last decade [5,6,14–20,23]. Most previous studies are case reports [18–20] or retrospective studies [5,6,14,16,17]. The present study is one of the few prospective studies performed in children from India. There were more male patients than female patients, and the male-to-female ratio was 1.4:1, which is probably due to higher prevalence of exposure to chiggers among boys, who like to play outdoors [2–5,14,16,23]. The mean age at presentation was 6.3 years, which is similar to that reported by Huang et al. [2]. The majority of cases occurred between September and February, which are the cooler months in this region. Similar observations have been recorded by other authors [3,4,10,15,17,18,23], whereas a study from Taiwan found the greatest number of cases between May and August [2].

Most of the children in the present study presented with fever (100%) and hepatomegaly (91%). The next most common manifestation was edema (60%). A previous study from Vellore reported edema in 37% of cases [15]. In our study, lymphadenopathy and an eschar were noted in 37% and 11% of cases, respectively, results that are similar to those of an earlier report [15]. In contrast, some studies outside India reported the presence of an eschar in 50–80% of cases [2,4,7]. Other authors did not find an eschar in any of their cases [6,16–19,23]. A maculopapular rash was found in 20% of the cases in our study. Other studies found a rash in 15–91% of their cases [2,4,7,10,16,17], whereas others did not observe a rash in any case [6]. Table 4 compares the complications reported in previous pediatric studies to those found in the present study.

A unique feature observed in this study was the high incidence of myocarditis, which was found in 34% of cases. These findings are in contrast to those of other pediatric studies. Two previous studies from India reported myocarditis in only 10–14.2% of their study subjects [17,24].

<table>
<thead>
<tr>
<th>Complications</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac dysfunction (myocarditis)</td>
<td>12</td>
<td>34</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>11</td>
<td>31</td>
</tr>
<tr>
<td>Platelet counts &lt;100,000/mm³</td>
<td>11</td>
<td>31</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>7</td>
<td>20</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>6</td>
<td>17</td>
</tr>
<tr>
<td>ARDS</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>DIC</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>Meningitis</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Peripheral gangrene</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 2 Complications of scrub typhus seen in the present study.
Table 3  Laboratory findings in children with scrub typhus.

<table>
<thead>
<tr>
<th>Biochemical parameters</th>
<th>No.</th>
<th>%</th>
<th>Hematologic parameters</th>
<th>No.</th>
<th>%</th>
<th>Serologic titers</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑Creatinine</td>
<td>7</td>
<td>20</td>
<td>TLC (per mm³)</td>
<td></td>
<td></td>
<td>OX-K</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>19</td>
<td>54</td>
<td>&lt;4000</td>
<td>1</td>
<td>3</td>
<td>1:80</td>
</tr>
<tr>
<td>↑AST/ALT</td>
<td>11</td>
<td>31</td>
<td>4000–11000</td>
<td>22</td>
<td>63</td>
<td>1:160</td>
</tr>
<tr>
<td>↑Alkaline phosphatase</td>
<td>10</td>
<td>29</td>
<td>&gt;11000</td>
<td>13</td>
<td>37</td>
<td>≥1:320</td>
</tr>
<tr>
<td>Bilirubin &gt; 1.2 mg/dl</td>
<td>3</td>
<td>9</td>
<td>Platelets (per mm³)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>6</td>
<td>17</td>
<td>&gt;150,000</td>
<td>11</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>↑CPK (MB)</td>
<td>12</td>
<td>34</td>
<td>100,000–150,000</td>
<td>14</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Albuminuria</td>
<td>1</td>
<td>3</td>
<td>&lt;100,000</td>
<td>11</td>
<td>31</td>
<td></td>
</tr>
</tbody>
</table>

case series from Thailand reported four cases of acute fulminant myocarditis in children with scrub typhus [25], whereas other studies did not find any case of myocarditis [2—5,10,15,16,18,19]. In fact, some authors have commented that scrub typhus myocarditis is not common and is not usually life-threatening [25]. Our study findings, however, indicate otherwise. All of the patients with myocarditis in our study also presented with cardiogenic shock and had elevated CPK-MB levels. CPK-MB is a highly specific marker for myocarditis, and determining the CPK-MB level is non-invasive [25]. Although the gold standard for diagnosing myocarditis is an endomyocardial biopsy, this procedure is invasive, and it is undesirable to perform biopsies on severely hemodynamically compromised patients [5]. Myocarditis in scrub typhus could be due to vasculitis, which may lead to end organ ischemic injury [1].

Another common complication was AKI, which was found in 20% of the cases. Two previous Indian studies based on pediatric data have reported incidences of AKI in rickettsial infections ranging from 2 to 4.7% [17,24]. Rickettsial infections have often been overlooked as a cause of AKI [26], especially in children. A recent retrospective study from central India did not report any case of AKI in children with rickettsial infections [14]. However, in adult studies, AKI has been described in 12—22% of cases [7,10]. Additionally, other case reports documented this complication [27,28]. The high incidence of AKI in our study could be due to the higher incidence of cardiogenic shock, which could have led to renal injury. Moreover, we defined AKI using the most recent consensus definition proposed by the AKIN [21], whereas other definitions were used previously. AKI that is caused by acute tubular necrosis is a result of direct invasion by Orientia tsutsugamushi [28].

The high incidences of myocarditis, shock and acute kidney injury that were observed in the present study have diagnostic and therapeutic implications. Many clinical features including fever, organomegaly, edema, hypotension, thrombocytopenia, coagulopathy, hepatitis, and hypoalbuminemia can also be caused by dengue infection, which results in diagnostic confusion. In fact, three of the patients in this study were started on a

Table 4  Comparison of various complications between the current study and previous pediatric studies (in percentages).

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Myocarditis</td>
<td>34</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>14.2</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Hepatitis</td>
<td>31</td>
<td>91.3</td>
<td>75</td>
<td>70.7</td>
<td>—</td>
<td>14.2</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Platelet counts &lt; 100,000/mm³</td>
<td>31</td>
<td>50</td>
<td>80</td>
<td>63.4</td>
<td>—</td>
<td>—</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>AKI</td>
<td>20</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>4.7</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>17</td>
<td>17.9</td>
<td>3.3</td>
<td>5</td>
<td>14.6</td>
<td>25</td>
<td>19</td>
<td>71</td>
</tr>
<tr>
<td>ARDS</td>
<td>9</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>18</td>
</tr>
<tr>
<td>DIC</td>
<td>9</td>
<td>—</td>
<td>—</td>
<td>0</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>8</td>
</tr>
<tr>
<td>Meningitis</td>
<td>6</td>
<td>21.4</td>
<td>3.3</td>
<td>5</td>
<td>12.2</td>
<td>25</td>
<td>19</td>
<td>64</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>3</td>
<td>7.1</td>
<td>36.7</td>
<td>85</td>
<td>12.2</td>
<td>8.3</td>
<td>9.5</td>
<td>4</td>
</tr>
<tr>
<td>Peripheral gangrene</td>
<td>3</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>51</td>
</tr>
</tbody>
</table>
fluid regimen as per the dengue management proto-
col. They developed volume overload within the
next few hours and required diuretics and inotropic
support. The presence of other indicators such
as the persistence of fever after the shock had
supervened, the absence of an increase in the
hematocrit, and the presence of an eschar helps
distinguish rickettsial infection from other hemor-
 rhagic fevers, such as dengue.

The Weil-Felix test, which detects heterophile antibodies to strains of Proteus sp., is inexpen-
sive and widely available and can be performed
rapidly to substantiate the diagnosis, especially in
resource-poor settings. Although the sensitivity of
the Weil-Felix test is relatively low, its specificity
is high [13,23]. In one particular study that evalu-
ated the various serological tests for scrub typhus,
the Weil-Felix test was found to have a sensitivity
of only 43% but a specificity of 98% for titers of 1:80
or more [25]. The Weil-Felix test is a helpful tool
that can be used to diagnose rickettsial infection
in appropriate clinical settings. Studies from other
parts of Asia have also indicated the usefulness of
this test when it is used in the correct clinical con-
text [10,11,13,16,17,19,23]. A positive correlation
was found between the results of the Weil-Felix
test and the detection of IgM antibodies using an
indirect immunofluorescence assay (IFA) in various
studies [13,29]. Most of the patients in this study
demonstrated a remarkable clinical response to
doxycline, as in other studies [1–5,10,14,16,23].
This dramatic response has also been used as a diag-
nostic test [10].

The present study has some limitations. First,
the study was performed in a tertiary referral hospi-
tal; therefore, the present data do not represent
the entire community, and the actual incidence of
rickettsiosis may be higher. Second, the Weil-
Felix test alone was used to confirm the diagnosis
because we did not have access to more sensi-
tive tests. The Weil-Felix test has low sensitivity
and may miss some cases of rickettsiosis. Because
we used the Weil-Felix test for diagnosis rather
than a more sensitive assay, many cases of scrub
typhus may have been missed and not included in
this study. If there were any significant clinical or
laboratory differences between the scrub typhus
patients who were OK-K positive and those who
were OK-K negative, this study may provide biased
results because it does not include OK-K negative
scrub typhus patients. Tests, such as IgM immuno-
fluorescence, could not be performed; such assays
are often not available in developing countries and
resource-poor settings. Despite these limitations,
we believe that this study may increase the aware-
ness of this treatable disease, especially among
clinicians, and may provide a better understanding
of the clinical manifestations and complications of
rickettsiosis, especially scrub typhus, in children.

A higher incidence of myocarditis and acute
kidney injury was observed in our study than in
previously published pediatric studies. This differ-
ence could be due to a delay in the diagnosis at the
peripheral health centers, which then led to late
referrals. Clinicians should be aware that myocar-
ditis is a serious cardiac manifestation of pediatric
rickettsiosis (including scrub typhus). The moni-
toring of vital signs, chest radiographs and ECG
changes should be performed for suspected cases
of myocarditis. CPK-MB and an echocardiogram can
help confirm damage to the myocardium and enable
the implementation of prompt therapeutic inter-
ventions.

Physicians should consider scrub typhus when
caring for patients with acute febrile illness in
demic areas [30]. Timely recognition of complica-
tions such as myocarditis, shock and acute
kidney injury in pediatric patients with ricket-
tsiosis, including scrub typhus, is of paramount
importance to ensure a favorable outcome.

Conclusions

1. Higher incidences of myocarditis and acute kid-
ney injury were observed in this study than were
found in previous pediatric studies. This differ-
ce could be due to the delay in diagnosis at the
peripheral health centers, which then led to a late
referral.
2. Clinicians should be aware that myocarditis is a
serious cardiac manifestation of pediatric rick-
ettioses (including scrub typhus).
3. The timely recognition of complications such as
myocarditis, shock and acute kidney injury in
patients, especially children, with rickettsioses,
including scrub typhus, is of paramount impor-
tance to ensure a favorable outcome.
4. A careful search for an eschar can help diagnose
rickettsiosis.

Contributors

All of the authors were involved in the management
of the patients. Manish Kumar and Sriram Krish-
amurthy reviewed the literature. Manish Kumar
and C.G. Delhikumar collected the data. Man-
ish Kumar and Sriram Krishnamurthy drafted the
manuscript. All authors approved the final version
of the manuscript.
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Competing interests

None stated.

References