Scrub Typhus with Sepsis and Acute Respiratory Distress Syndrome

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Scrub typhus is a major infectious threat in the Asia-Pacific region. We report an unusual case of scrub typhus in a patient in Singapore who presented with sepsis and acute respiratory distress syndrome but lacked the pathognomonic eschar. The patient recovered after appropriate diagnosis and doxycycline treatment. Rickettsial diseases should be included in the differential diagnosis of febrile illnesses in regions where the diseases are endemic, and absence of eschar should not be the criterion used to rule out scrub typhus.

On 3 October 2011, a 35-year-old male became acutely ill and was admitted to a hospital in a neighboring country following 4 days of an undifferentiated febrile illness. On admission, the patient had fever, chills, giddiness, nonspecific abdominal pain, cough with nonpurulent sputum, and lethargy. His condition rapidly deteriorated, requiring mechanical ventilation for respiratory distress, followed by septic shock on the third day of hospitalization. He received empirical intravenous moxifloxacin and meropenem, oral clarithromycin, and vasopressor support. As his condition did not improve, he was transferred to Singapore on day 4 of hospitalization.

On admission in Singapore on 6 October 2011, the patient was febrile (38.0°C) with a blood pressure of 120/63 mmHg supported by 2 μg/kg/min of dopamine. His oxygen saturation was 97% with a fraction of inspired O2 of 60%. Physical examination disclosed procalcitonin level tests on day 6 after admission showed much.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC count (mm⁻³)</td>
<td>12.3 × 10³ (↑)</td>
<td>(4–11) × 10³</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>74</td>
<td>54–62</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>9 (↓)</td>
<td>15–40</td>
</tr>
<tr>
<td>Hemoglobin level (g/dl)</td>
<td>11 (↓)</td>
<td>11.5–16.5</td>
</tr>
<tr>
<td>Prothrombin time (s)</td>
<td>11.1</td>
<td>11–13.5</td>
</tr>
<tr>
<td>Partial thromboplastin time (s)</td>
<td>37.8</td>
<td>25–35</td>
</tr>
<tr>
<td>Platelet count (μl⁻¹)</td>
<td>87 × 10³ (↓)</td>
<td>(140–440) × 10³</td>
</tr>
</tbody>
</table>

| Blood chemistry | | |
| ALT level (U/liter) | 113 (↑) | <37 |
| AST level (U/liter) | 140 (↑) | <41 |
| Bilirubin level (μmol/liter) | 22 | 3–24 |
| Albumin level (g/liter) | 24 (↓) | 35–50 |
| Creatinine level (μmol/liter) | 154 (↑) | 44–110 |
| CRP level (mg/liter) | 181.9 (↑) | <10 |

a WBC, white blood cell.

ALT, alanine aminotransferase.

AST, aspartate aminotransferase.

CRP, C-reactive protein.

↑, value above normal reference range.

↓, value below normal reference range.

He was empirically treated with oral oseltamivir, doxycycline, intravenous amoxicillin-clavulanate, and ceftazidime. He became afebrile 48 h after admission in Singapore. Bronchoalveolar lavage was performed on day 2 after admission, and cultures were sterile. In view of his severe ARDS, intravenous hydrocortisone, beginning with an initial dose of 100 mg every 8 h, was initiated on day 3 after admission and subsequently tapered off. Chest radiography and laboratory marker (C-reactive protein, procalcitonin) level tests on day 6 after admission showed much improvement. He was successfully weaned from mechanical ventilatory support on day 7.

Serum samples taken on day 9 of illness were tested with a recently developed Western blot assay (developed at the U.S. Naval Medical Research Center [NMRC]) that can recognize and differentiate various febrile illnesses of bacterial origin (our un-
Rickettsial DNA (2,3). The PCR was performed with whole blood (our unpublished data). PCR is considered a very sensitive and specific method for the detection of Orientia tsutsugamushi. The recombinant antigens/whole-cell antigens derived from various pathogens had been tested for specificity against 15 different bacterial species tested for, except O. tsutsugamushi. The serum was negative for all of the pathogens tested for, except O. tsutsugamushi (Fig. 1A and B), and a mixture of recombinant 56-kDa antigens (1) derived from the most prevalent serotypes of O. tsutsugamushi (Karp, Kato, Gilliam, and TA763) was detected. O. tsutsugamushi infection was further verified by an in-house-developed real-time PCR assay that detects the 56-kDa protein-encoding gene. This real-time PCR assay was sensitive enough to detect as few as 10 genomic equivalents of O. tsutsugamushi and had been tested for specificity against 15 different bacterial species with no cross-reactivity, demonstrating 100% specificity for O. tsutsugamushi (our unpublished data). PCR is considered a very sensitive and specific method for the detection of O. tsutsugamushi rickettsial DNA (2, 3). The PCR was performed with whole blood taken from the patient on day 9 of illness (at DSO National Laboratories, Singapore). The primers and probe used were forward primer 5’-GTTGTCGTTGCCGTTTTCA-3’, reverse primer 5’-TGGATCCAAGCGAGCAGA-3’, and TaqMan probe 5’-(6-carboxyfluorescein)-TAGTGCGATAGAATTGGATGAT GAAGGA-(Black Hole Quencher 1)-3’.

In this report, we present the case of a patient with clinically severe scrub typhus who was hospitalized in Singapore with the complication of sepsis syndrome with ARDS. However, no characteristic eschar was present and the patient recovered completely with timely diagnosis and treatment. Improvement in the health of the patient was observed from admission, as doxycycline ther-
apy was initiated on day 1 after his transfer to Singapore. While most patients with scrub typhus present with a relatively mild illness, this case illustrates its potential to cause severe clinical manifestations.

Scrub typhus is an acute febrile illness caused by the obligate mite-borne Gram-negative bacterium *O. tsutsugamushi* (family Rickettsiaceae). It is endemic to the Tsutsugamushi Triangle of the Asia-Pacific region (4), accounts for 23% of all febrile illness in that region, and can have a mortality rate of up to 35% if left untreated (1). The disease is an important public health problem (5–9), and an estimated one billion people live in areas at risk for scrub typhus with an estimated one million annual cases (10). Scrub typhus was the most notable rickettsiosis affecting U.S. troops in WWII in the China-Burma-India theater of operations and had a higher mortality rate than any other infectious disease there (8). Many new or imported cases of scrub typhus have also been reported from regions outside the traditional Asia-Pacific region (11–13).

Scrub typhus, like most rickettsial diseases, is generally difficult to diagnose because it produces clinical characteristics similar to those of many other tropical febrile illnesses. The clinical severity of scrub typhus ranges from mild febrile illness to a fatal outcome. Complications may include encephalitis, interstitial pneumonia, hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency, ARDS, acute renal failure, myocarditis, septic shock, and death (14, 15). Pulmonary involvement frequently occurs in mild cases and is the principal cause of death in severe disease (6, 7). Severe complications such as sepsis and ARDS are typically the results of delayed diagnosis and treatment. When treated with an appropriate antibiotic (doxycycline, tetracycline, or chloramphenicol), patients typically become afebrile within 48 h.

This patient was a vegetable farm supervisor with no significant medical or travel history. An increase in rat infestation was noted at the farm where he worked in the weeks leading to his illness. He subsequently reported having noticed a dead rat in his car, which he removed with his bare hands about a week prior to falling ill. While the patient’s history and clinical presentation were suggestive of a scrub typhus diagnosis, he did not have the pathognomonic eschar.

The patient did not respond to quinolone and macrolide therapy. Scrub typhus is well known to be unresponsive or show only a suboptimal response to quinolones, beta-lactams, penicillins, clarithromycin, and cephalosporins (8, 16, 17), and in northern Thailand, there has been a reported case of resistance to chloramphenicol and doxycycline (18). It is also notable that the Widal, Weil-Felix test, a generally used diagnostic test for rickettsial diseases, showed a negative result with the patient sample. This result is not surprising, as it is well known that the Widal, Weil-Felix test is not very sensitive for the diagnosis of scrub typhus (19).

Although Singapore is a major economic hub attracting a large number of travelers, there are only scant published reports of the prevalence of rickettsial disease in Singapore (13, 20–23). Because scrub typhus is endemic in countries neighboring Singapore, health care providers must be aware of a patient’s travel history. While clinical signs such as lymphadenopathy, splenomegaly, rash, and fever are nonspecific, an eschar, if present, is pathognomonic in the diagnosis of scrub typhus. However, eschars are rare among Southeast Asian patients (24). The nonspecific presentation of patients and the absence of a characteristic eschar make misdiagnosis and underreporting of scrub typhus common.

This study underscores the importance of including scrub typhus and other rickettsial diseases in the differential diagnosis of patients with acute febrile illnesses of unknown origin in this region. Although eschar is a pathognomonic feature of scrub ty-
plus, its absence does not rule out scrub typhus. Awareness of unusual manifestations of scrub typhus such as sepsis syndrome and ARDS and the timely administration of empirical treatment with doxycycline in suspicious cases can greatly help to decrease the morbidity and mortality associated with rickettsial diseases.

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We have no conflict of interest to declare.

REFERENCES