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, nonspicific 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 no significant rash. His abdomen was flushed, soft, and non-tender. Chest auscultation revealed bilateral crepitations.

A chest radiograph showed bilateral alveolar shadows consistent with acute respiratory distress syndrome (ARDS). Abdominal sonography and echocardiography findings were normal. Laboratory data (Table 1) revealed leukocytosis, thrombocytopenia, elevated aspartate aminotransferase and alanine aminotransferase levels, and mild renal impairment. He was diagnosed with sepsis syndrome complicated by ARDS. The differential diagnosis included melioidosis, leptospirosis, rickettsiosis, and viral infections, including influenza virus. Serologic tests for hantavirus, melioidosis, dengue virus, *Leptospira*, chikungunya virus, *Nipah* virus, and *Mycoplasma* were negative. Urine, blood, and sputum cultures also were negative for *Legionella* and pneumococcal antigens. A Widal, Weil-Felix test (agglutination test for the diagnosis of rickettsial infections) was also performed with a serum sample (taken on 6 October 2011) but was negative (all titers were less than 1:40). 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-

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
<th>Reference range</th>
</tr>
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<tbody>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
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<tr>
<td>WBC count (mm⁻³)</td>
<td>12.3 × 10⁹</td>
<td>(4–11) × 10⁹</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>
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<tr>
<td>Prothrombin time (s)</td>
<td>11.1</td>
<td>11–13.5</td>
</tr>
<tr>
<td>Partial thromboplastin time (s)</td>
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<td>25–35</td>
</tr>
<tr>
<td>Platelet count (μl⁻¹)</td>
<td>87 × 10⁹</td>
<td>(140–440) × 10⁹</td>
</tr>
<tr>
<td>Blood chemistry</td>
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<td></td>
</tr>
<tr>
<td>ALT level (U/liter)</td>
<td>113 (↑)</td>
<td>&lt;37</td>
</tr>
<tr>
<td>AST level (U/liter)</td>
<td>140 (↑)</td>
<td>&lt;41</td>
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<tr>
<td>Bilirubin level (μmol/liter)</td>
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<td>3–24</td>
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<tr>
<td>Albumin level (g/liter)</td>
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<tr>
<td>Creatinine level (μmol/liter)</td>
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<td>44–110</td>
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<tr>
<td>CRP level (mg/liter)</td>
<td>181.9 (↑)</td>
<td>&lt;10</td>
</tr>
</tbody>
</table>

a WBC, white blood cell.

b ALT, alanine aminotransferase.

c AST, aspartate aminotransferase.

d CRP, C-reactive protein.

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Received 19 February 2013 Returned to modification 28 March 2013 Accepted 26 May 2013 Published ahead of print 12 June 2013

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August 2013 Volume 51 Number 8 Journal of Clinical Microbiology p. 2787–2790
published data). The serum testing was performed at the Emerging Infectious Diseases Division, Duke-NUS Graduate Medical School, Singapore, for murine typhus, spotted fever, scrub typhus, Q fever, and leptospirosis. The assay uses recombinant antigens/whole-cell antigens from various pathogens (Rickettsia typhi, R. conorii, Orientia tsutsugamushi, Coxella burnetii, and Leptospira interrogans). 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. Figure 1C represents the protein gel showing the presence of various recombinant/whole-cell antigens used in the Western blot assay. Figure 1D and E show the positive-control Western blot assays detecting these antigens in the serum of a confirmed scrub typhus patient. The results of the SCRUBS assay were confirmed by a 4-fold titer increase and isolation of O. tsutsugamushi from a serum sample. Panel D shows IgG results, and panel E shows IgM results. The values to the left of panels C to E are molecular sizes in kilodaltons.

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’-GGTTATGGCCTGCGCT-3’, reverse primer 5’-TCATGCAACGCGACG-3’, and TaqMan probe 5’-(6-carboxyfluorescein)-TTAGTTCTGATAGAATTGGATGAT GAAGGA-(Black Hole Quencher 1)-3’. The real-time PCR conditions used were 95°C for 2 min and 50 cycles of 95°C for 0 s, 60°C for 6 s, and 72°C for 12 s. Figure 2 shows the fluorescence profile (relative fluorescence units) representing positive detection of the O. tsutsugamushi 56-kDa rickettsial antigen gene in a whole-blood sample (sample 2); a serum sample (sample 1) was negative. The values to the left of panels C to E are molecular sizes in kilodaltons.

In view of the confirmed scrub typhus diagnosis, oseltamivir, intravenous amoxicillin-clavulanate, and cefazidime were stopped and the patient received 2 weeks of oral doxycycline (100 mg twice daily) and recovered completely. He was discharged from the hospital on day 11 following admission.

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 the-
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 typhus, it is not a consistently present finding, and the absence of an eschar does not exclude the diagnosis of scrub typhus. Therefore, clinicians should maintain a high index of suspicion for scrub typhus in patients with acute febrile illness, especially in endemic regions.
phus, 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.

ACKNOWLEDGMENTS
This study was supported in part by a Duke-NUS signature research program funded by the Agency for Science, Technology and Research (A*STAR), Singapore, and the Ministry of Health, Singapore, and by work unit no. 6000.RAD1.J.A0310 (NMRC).

The opinions and assertions contained herein are ours and are not to be construed as official or as reflecting the views of the Department of the Navy, the Naval Service at large, the Department of Defense, or the U.S. Government. C.-C.C. and W.M.C. are employees of the U.S. Government. This work was prepared as part of official duties. Title 17 U.S.C. §101 defines a U.S. Government work as work prepared by an employee of the U.S. Government as part of that person’s official duties, and “copyright protection under this title is not available for any work of the United States Government.”

We thank Goh Liang Kee (Duke-NUS) for assistance with statistical analysis. C.-C.C. and W.M.C. thank Zhiwen Zhang for her effort in developing the Western blot assay using recombinant proteins.

We have no conflict of interest to declare.

REFERENCES