ACUTE RESPIRATORY DISTRESS SYNDROME IN SCRUB TYPHUS

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Abstract. Scrub typhus is a mite-borne infectious disease caused by Orientia tsutsugamushi. Acute respiratory distress syndrome (ARDS) is a serious complication of scrub typhus. This study retrospectively reviewed the medical records of 72 patients diagnosed with scrub typhus from January 1998 to August 2006 in Kaohsiung Chang Gung Memorial Hospital in Taiwan. Eight of 72 scrub typhus patients with ARDS were included in the study; the other patients without ARDS were used as controls. The mortality rate for the scrub typhus patients with ARDS was 25%. The eight patients seldom had underlying diseases. Initial presentations of dyspnea and cough, white blood cell count, hematocrit, total bilirubin, and delayed use of appropriate antibiotics use were significant predictors of ARDS. Multivariate analysis showed that albumin, prothrombin time, and delayed use of appropriate antibiotics were independent predictors of ARDS. Identification of these relative risk factors may help clinicians evaluate clinical cases of scrub typhus with ARDS.

INTRODUCTION

Scrub typhus is a mite-borne infectious disease caused by Orientia tsutsugamushi (previously known as Rickettsia tsutsugamushi). The disease is distributed throughout the Asia Pacific rim and is endemic in South Korea, China, Taiwan, Japan, Pakistan, India, Thailand, Malaysia, and northern Australia. Scrub typhus is an acute febrile disease characterized by a typical primary necrotic lesion (eschar), generalized lymphadenopathy, rash, and non-specific symptoms such as fever, headache, myalgia and cough. Severe complications include prominent encephalitis, interstitial pneumonia, acute respiratory distress, myocarditis and pericarditis, cardiac arrhythmia, acute renal failure, acute hepatic failure, and acute hearing loss. Acute respiratory distress syndrome (ARDS) is a serious complication of scrub typhus. However, few case reports of scrub typhus and no cohort studies of scrub typhus complicated by ARDS have been reported.

Taiwan has been endemic for scrub typhus for many decades. In southern Taiwan, many scrub typhus patients are admitted to Kaohsiung Chang Gung Memorial Hospital, a 2,500-bed hospital that is the largest tertiary medical center in southern Taiwan. This study retrospectively analyzed the medical records of scrub typhus patients admitted to Kaohsiung Chang Gung Memorial Hospital. The goal of the present study was to investigate the clinical course and outcome of scrub typhus patients with ARDS and to identify the relative risk factors for acquiring ARDS in scrub typhus patients. Identification of relative risk factors may help clinicians evaluate the clinical course of scrub typhus complicated by ARDS.

MATERIALS AND METHODS

The study protocol was reviewed and approved by the Institutional Review Board of Kaohsiung Chang Gung Memorial Hospital. This study retrospectively reviewed the medical records of 72 patients diagnosed with scrub typhus between January 1998, and August 2006, in Kaohsiung Chang Gung Memorial Hospital. Quality assurance procedures for diagnostic tests for the 72 scrub typhus patients were conducted by the Center for Disease Control (Taipei, Taiwan) based on a polymerase chain reaction (PCR) or serologic analysis for indirect microimmunofluorescent antibody (IFA) for O. tsutsugamushi. Diagnostic IFA results were positive for O. tsutsugamushi if the total antibody titer for the Karp, Kato, and Gilliam strains of O. tsutsugamushi showed a ≥ 4-fold increase in paired positive serum samples or the antibody titer for IgM was ≥ 1:80. A diagnosis of ARDS was based on the criteria for ARDS of the American-European Consensus Committee: 1) acute onset timing; 2) chest radiograph showing bilateral lung infiltrates; 3) severe hypoxia with a partial pressure of arterial oxygen to fraction of inspired oxygen ratio (PaO2/FiO2) ≤ 200 mm of Hg, regardless of the level of positive end-expiratory pressure; and 4) no clinical evidence of increased left atrial pressure with a pulmonary arterial wedge pressure ≤ 18 mm of Hg.

Patients with scrub typhus complicated by ARDS (n = 8) comprised the ARDS group. Scrub typhus patients with no ARDS complications were grouped as controls (n = 64). Demographic characteristics and clinical manifestations were recorded. Laboratory data recorded upon admission of each patient, which included white blood cell (WBC) count, hematocrit (Hct), hemoglobin (Hb) level, platelet counts, prothrombin time (PT), activated partial thromboplastin time (APTT), and blood urea nitrogen (BUN), creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total bilirubin, and albumin (ALB) levels, were obtained from medical records. Data regarding microorganisms identified by blood culture and antibiotics administered were also obtained from medical records.

An antibiotic day (A day) was defined as the day when appropriate treatment with antibiotics (tetracyclines or chloramphenicol) was begun for patients with scrub typhus complicated by ARDS after illness onset (defined as the time the fever began). An intubation day (I day) was defined as the day when the scrub typhus patient with ARDS was intubated after illness onset (beginning of fever).
incline. Acute hepatic failure was defined as encephalopathy or jaundice with a marked increase in liver enzyme levels (AST and ALT). Upper gastrointestinal bleeding was defined as hematemesis or tarry stool passage that was confirmed by panendoscopy.

**Statistical analysis.** Data were collected and analyzed with SPSS for Windows version 13.0 (SPSS Inc., Chicago, IL). Quantitative variables are presented as means ± SD. Statistical significance of univariate analysis was determined by an independent-sample t-test or a Mann-Whitney U test for continuous variables. A chi-square test was used to determine dichromatic variables. Differences were considered statistically significant when \( P < 0.05 \).

RESULTS

Eight of 72 (11.1%) scrub typhus patients had ARDS. Sixty-four scrub typhus patients without ARDS were used as controls. Table 1 summarizes the characteristics and clinical course of the eight (three males and five females ) scrub typhus patients with ARDS. The mean ± SD age of the eight patients was 55.38 ± 21.51 years (range = 24–75 years). The mortality rate for the subjects was 25% (2 of 8). Three patients had no underlying diseases, three had chronic obstructive pulmonary disease (COPD), one had diabetes mellitus, one had hypertension, one had gout, and one was thirty-one weeks pregnant. The two most common complications in the study population were acute hepatic failure (6 of 8, 75%) and upper gastrointestinal bleeding (5 of 8, 62.5%). Two subjects had acute renal failure (25%), two had pneumonia (25%), two had urinary tract infection (25%), one had a central venous pressure line infection (12.5%), one had pre-eclampsia (12.5%), and one had a seizure (12.5%). None of the scrub typhus patients with ARDS were initially treated with tetracyclines or chloramphenicol. The mean ± SD A day was day 8.25 ± 5.05 (range = days 2–16). The mean ± SD I day was day 6.88 ± 3.64 (range = days 4–14). The mean ± SD duration of ventilation support was 14.75 ± 10.40 days (range = 7–35 days).

Table 2 shows a presents a comparison of sex, age, and underlying diseases between subjects with ARDS and subjects without ARDS. Underlying diseases were seldom noted in subjects with or without ARDS. Other than COPD (37.5%), the percentage of all underlying diseases was less than 15%. Furthermore, the ARDS group and the control group did not significantly differ in sex, age, or underlying disease.

Table 3 summarizes the clinical presentations of scrub typhus patients with ARDS and those without ARDS. In addition to fever, the most common clinical presentations for scrub typhus patients with ARDS were cough (100%) and dyspnea (87.5%); there were significant differences in cough \( (P = 0.001) \) or dyspnea \( (P < 0.001) \) between the ARDS group and the control group.

Table 4 shows a summary of initial laboratory findings for subjects with and without ARDS and compares characteristics and initial laboratory findings between the ARDS group and the control group. The ARDS group did not significantly differ from the control group in platelet count, Hb level, PT, APTT, and BUN, creatinine, AST, ALT, ALP, or albumin levels. However, the ARDS group differed significantly from the control group in WBC count \( (P = 0.018) \), Hct \( (P = 0.047) \), and total bilirubin level \( (P = 0.050) \).

Table 5 compares appropriate antibiotics course (tetracyclines or chloramphenicol) in scrub typhus patients with ARDS and without ARDS. The mean ± SD A day for the

### Table 1

Characteristics and clinical course of eight scrub typhus patients with ARDS*

<table>
<thead>
<tr>
<th>No.</th>
<th>Age (years), Sex</th>
<th>Underlying diseases</th>
<th>Complications</th>
<th>Antibiotics course</th>
<th>A day</th>
<th>1 day</th>
<th>Duration of ventilation</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>66, F</td>
<td>None</td>
<td>Acute hepatic failure</td>
<td>Penicillin plus ceftriaxone, doxycycline</td>
<td>Day 14</td>
<td>Day 9</td>
<td>7 days</td>
<td>Survived</td>
</tr>
<tr>
<td>2</td>
<td>70, F</td>
<td>HTN</td>
<td>Acute hepatic failure, Urinary tract infection</td>
<td>Cefamazin plus gentamicin, Oxytetracycline</td>
<td>Day 9</td>
<td>Day 4</td>
<td>9 days</td>
<td>Survived</td>
</tr>
<tr>
<td>3</td>
<td>71, M</td>
<td>COPD</td>
<td>Acute hepatic failure, UGI bleeding</td>
<td>Piperacillin plus amikacin, doxycycline</td>
<td>Day 2</td>
<td>Day 3</td>
<td>13 days</td>
<td>Survived</td>
</tr>
<tr>
<td>4</td>
<td>44, F</td>
<td>None</td>
<td>Acute hepatic failure, Urinary tract infection, CVP line infection</td>
<td>Penicillin plus ceftriaxone, doxycycline, Clindamycin</td>
<td>Day 7</td>
<td>Day 8</td>
<td>27 days</td>
<td>Survived</td>
</tr>
<tr>
<td>5</td>
<td>24, F</td>
<td>Pregnancy (31 weeks)</td>
<td>Acute hepatic failure, UGI bleeding, Pre-eclampsia</td>
<td>Penicillin plus ceftriaxone, oxytetracycline</td>
<td>Day 2</td>
<td>Day 5</td>
<td>10 days</td>
<td>Survived</td>
</tr>
<tr>
<td>6</td>
<td>24, F</td>
<td>None</td>
<td>Acute hepatic failure, Seizure, UGI bleeding, Pneumonia</td>
<td>Levofloxacin, Doxycycline, Ceftriaxone plus Amikacin, Doxycycline, Teicoplanin</td>
<td>Day 7</td>
<td>Day 8</td>
<td>8 days</td>
<td>Survived</td>
</tr>
<tr>
<td>7</td>
<td>75, M</td>
<td>COPD</td>
<td>Acute hepatic failure, UGI bleeding</td>
<td>Penicillin plus Ceftriaxone, Doxycycline, Cefotioxime</td>
<td>Day 16</td>
<td>Day 14</td>
<td>9 days</td>
<td>Died</td>
</tr>
</tbody>
</table>

*ARDS = acute respiratory distress syndrome; A day = the day when antibiotic use was started; 1 day = the day when the patient was intubated after the onset of illness; HTN = hypertension; UGI = upper gastrointestinal; COPD = chronic obstructive pulmonary disease; CVP = central venous pressure; DM = diabetes mellitus.
Infection, without direct invasion of the organism, 4.

Additional clinical onset). Duration of complications in scrub typhus patients (Table 6).

Comparisons of underlying diseases in scrub typhus patients with ARDS (ARDS group) and without ARDS (control group) *

<table>
<thead>
<tr>
<th>Symptom/sign</th>
<th>ARDS group (n = 8)</th>
<th>Control group (n = 64)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>8 (100)</td>
<td>62 (96.9)</td>
<td>1.000</td>
</tr>
<tr>
<td>Rash</td>
<td>3 (37.5)</td>
<td>24 (37.5)</td>
<td>1.000</td>
</tr>
<tr>
<td>Bone pain</td>
<td>0 (0.0)</td>
<td>9 (14.1)</td>
<td>0.584</td>
</tr>
<tr>
<td>Myalgia</td>
<td>0 (0.0)</td>
<td>5 (7.8)</td>
<td>1.000</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>7 (87.5)</td>
<td>9 (14.1)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Cough</td>
<td>8 (100)</td>
<td>25 (39.1)</td>
<td>0.001</td>
</tr>
<tr>
<td>Chest pain</td>
<td>2 (25.0)</td>
<td>7 (10.9)</td>
<td>0.260</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>3 (37.5)</td>
<td>28 (43.8)</td>
<td>1.000</td>
</tr>
<tr>
<td>Headache</td>
<td>2 (25.0)</td>
<td>26 (40.6)</td>
<td>0.471</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1 (12.5)</td>
<td>19 (29.7)</td>
<td>0.429</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (12.5)</td>
<td>12 (18.6)</td>
<td>1.000</td>
</tr>
<tr>
<td>Tarry stool</td>
<td>2 (25.0)</td>
<td>5 (7.8)</td>
<td>0.171</td>
</tr>
<tr>
<td>Conscious drowsy</td>
<td>1 (12.5)</td>
<td>3 (4.7)</td>
<td>0.382</td>
</tr>
<tr>
<td>Eschar</td>
<td>5 (62.5)</td>
<td>42 (65.6)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

* An individual patient might have more than one symptom and/or sign; ARDS = acute respiratory distress syndrome.

ARDS group was day 8.25 ± 5.01, which was later than that of the control group (day 5.05 ± 2.79) (P = 0.059). The mean ± SD duration of antibiotics use in the ARDS group was 13.88 ± 4.19 days, which was longer than that of the control group (9.25 ± 3.35 days) (P = 0.002).

Multivariate analysis showed that a low level of ALB, prolonged PT, and delayed treatment with antibiotics were independent predictive variables associated with ARDS complications in scrub typhus patients (Table 6).

DISCUSSION

This retrospective study showed that 11.1% of the 72 scrub typhus patients had ARDS complications. The mortality rate for the eight scrub typhus patients with ARDS was 25% (2 of 8). Whether this mortality rate for patients with scrub typhus complicated by ARDS assessed at a medical center reflect the population was likely biased by patient selection and referral patterns. Scrub typhus complicated by ARDS has seldom been discussed; few case reports and only one short communication report have been published.

The pathologic progression of ARDS reflects the sequential occurring exudative, organizing (fibroproliferative) and fibrotic stages. Park and others reported diffuse alveolar damage in the organizing stage without evidence of vasculitis. Additional clinical studies are needed to increase awareness of ARDS in scrub typhus patients. Consequently, clinicians are likely not aware of the potential for ARDS when treating scrub typhus patients at high risk for ARDS.

The pulmonary manifestations of scrub typhus are varying grades of bronchitis and interstitial pneumonitis progressing to ARDS. Acute respiratory distress syndrome is defined as an acute and persistent lung inflammation with increased vascular permeability and is most often associated with sepsis syndrome, aspiration, primary pneumonia, or multiple traumas.

The pathologic progression of ARDS reflects the sequentially occurring exudative, organizing (fibroproliferative) and fibrotic stages. Park and others reported diffuse alveolar damage in the organizing stage without evidence of vasculitis. Immunologic response of the lung to previous O. tsutsugamushi infection, without direct invasion of the organism, might have been involved in the pathogenesis.

Other than COPD (37.5%) in the ARDS group, the incidence of other underlying diseases was low (less than 20%) in the current study; furthermore, no history of stroke was noted.

Comparisons of appropriate antibiotics course (tetracyclines or chloramphenicol) in scrub typhus patients with ARDS (ARDS group) and without ARDS (control group) *

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>ARDS group (n = 8)</th>
<th>Control group (n = 61)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetracyclines</td>
<td>6 (75.0)</td>
<td>52 (85.2)</td>
<td>0.535</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>2 (25.0)</td>
<td>9 (14.8)</td>
<td>0.260</td>
</tr>
<tr>
<td>Duration (days)</td>
<td>13.88 ± 4.19</td>
<td>9.25 ± 3.35</td>
<td>0.002</td>
</tr>
</tbody>
</table>

* ARDS = acute respiratory distress syndrome; COPD = chronic obstructive pulmonary disease.
in either group of scrub typhus patients. One possible reason is that scrub typhus is a mite-borne infectious disease caused by *O. tsutsugamushi*. Almost all subjects had a history of traveling to areas endemic for scrub typhus, which indicates that most patients with scrub typhus have the resilience to survive extensive travel.

Scrub typhus may begin insidiously with headache, anorexia, or malaise. In some cases, scrub typhus appears abruptly with chills and fever; rash and eschar may also be present. Respiratory problems are often present; 45% of the patients in one study had a cough. In the control group of the current study, fever, cough, rash, and eschar were observed in 96.9%, 39.1%, 37.5% and 65.6% of the study population, respectively. These findings are consistent with findings of previous reports. However, some clinical manifestations in the 64 control patients differed from those reported elsewhere: incidence of myalgia (7.8%) and headache (40.6%) were lower than those previously reported. Clinical presentations of the respiratory system (cough and dyspnea) were the most significant differences between the ARDS group and the control group in the current study. A reasonable conclusion is that scrub typhus patients should be carefully evaluated for potential progression to ARDS if they initially have respiratory symptoms.

The WBC counts of the ARDS group were significantly higher than those of the control group, which indicated that the ARDS group was more seriously infected than the control group. Hematocrit in the ARDS group was significantly lower than that of the control group, which suggested that the ARDS group was more anemic than the control group. Although all liver enzyme levels (AST, ALT, ALP, and total bilirubin) were increased in both the ARDS and control groups, only the total bilirubin level was significantly higher in the ARDS group than in the control group. A scrub typhus patient with severe infection, anemia, and jaundice may be considered to be at high risk for developing ARDS.

Treatment with doxycycline or chloramphenicol usually lowers fever within 24 hours. Doxycycline may be more effective for rapidly ameliorating symptoms. In the current study, one patient was treated with oxytetracycline and seven were treated with doxycycline in the ARDS group. In the control group, five patients were treated with oxytetracycline, fifty-four were treated with doxycycline, and two were treated with chloramphenicol. Three patients in the control group were not treated with doxycycline or chloramphenicol.

The optimal duration of therapy is uncertain. In a study with three days of therapy, short courses of doxycycline or chloramphenicol are associated with an increased risk of relapse. However, a study of a larger population reported short-course therapy to be effective; in this multicenter trial, patients with scrub typhus randomly received seven days of treatment with tetracycline or three days of treatment with doxycycline.

Scrub typhus lasts for 14–21 days without treatment. Serious complications of scrub typhus generally occur in the second week of an untreated illness. In contrast, scrub typhus patients treated with appropriate antibiotics (tetracyclines or chloramphenicol) typically become afebrile within 48 hours of starting therapy. In the present study, the mean ± SD day of appropriate antibiotics treatment in the ARDS group was day 8.25 ± 5.01, which was significantly later than that in the control group (day 5.05 ± 2.79) (\(P = 0.059\)). The mean ± SD I day (day 6.88 ± 3.64, range = days 4–14) was earlier than the mean ± SD A day (day 8.25 ± 5.01, range = days 2–16) (Table 1). The mean ± SD duration of appropriate antibiotics in the ARDS group (13.88 ± 4.19 days) was significantly longer than that in the control group (9.25 ± 3.35 days). It may be concluded that scrub typhus patients are at high risk for developing ARDS if appropriate antibiotics treatment is delayed, and scrub typhus patients with ARDS need a longer course of antibiotics than those without ARDS. Therefore, early use of appropriate antibiotics is vital.

Survival of ARDS patients improved over time. Mortality of these patients is currently estimated to be approximately 35–40%. Respiratory failure is unusual as a direct cause of death. In one study of 47 patients, death during the first 3 days usually resulted from an underlying cause of ARDS, not respiratory failure. In the same study, nosocomial infections and sepsis accounted for most deaths. In the present study, the mortality rate of scrub typhus patients with ARDS was 25% (2 of 8), which was lower than the mortality rate for ARDS caused by other microorganisms. The two deaths in our study may have been caused by a delay in appropriate treatment (day 9 and day 16) and multiple organ failure (Table 1).

In the current study, multivariate analysis showed that an ALB level, a prolonged PT and delayed treatment with antibiotics were independently predictive variables. Because of the limitation of the statistical software (SPSS for Windows version 13.0), only variables regarding age, sex, A day, and initial laboratory data were used in the multivariate analysis.

This retrospective study had several limitations. First, this study was conducted at one medical center, and the patient population may be biased by patient selection and referral pattern. Second, this study was a retrospective survey, which not only resulted in incomplete data for some patients, but also did not control for laboratory examinations and clinical courses of all scrub typhus patients. Additional prospective investigations should be conducted. Despite these limitations, this study provides relatively rare data regarding a series of scrub typhus patients with ARDS.

In conclusion, scrub typhus, a mite-borne infectious disease caused by *O. tsutsugamushi*, is distributed throughout the Asia Pacific rim and can appear in a wide range of clinical manifestations, ranging from a mild febrile illness to life-threatening complications. In scrub typhus patients, ARDS is one of the most serious complications. This study analyzed scrub typhus patients with ARDS. Univariate analysis showed that initial symptoms of dyspnea and cough, higher WBC counts, lower hematocrits, higher total bilirubin counts, and delayed treatment with appropriate antibiotics were significantly predictive variables associated with scrub typhus patients with ARDS. Multivariate analysis showed that low

<table>
<thead>
<tr>
<th>TABLE 6</th>
<th>Multivariable analysis of associated risk factors for scrub typhus patients with complicated ARDS*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( P )</td>
</tr>
<tr>
<td>ALB (g/dL)</td>
<td>0.006</td>
</tr>
<tr>
<td>PT (sec)</td>
<td>0.028</td>
</tr>
<tr>
<td>A day (days)</td>
<td>0.013</td>
</tr>
</tbody>
</table>

*ARDS = acute respiratory distress syndrome; CI = confidence interval; ALB = albumin; PT = prothrombin time; A day = the day when antibiotic use (tetracyclines or chloramphenicol) was started after illness onset (fever onset).
ALB levels, prolonged PT, and delayed treatment with appropriate antibiotics were independent predictive variables associated with scrub typhus complicated by ARDS.

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