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Original Article

Patients with Acute Respiratory Distress Syndrome Caused by Scrub Typhus: Clinical Experiences of Eight Patients

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Background: The aim of this study is to describe the clinical course and outcome of patients who were diagnosed with acute respiratory distress syndrome (ARDS) caused by scrub typhus and who received ventilator care in the intensive care units (ICU) of two university hospitals.
Methods: We performed a retrospective analysis of all adult ventilated patients who were diagnosed with ARDS caused by scrub typhus.
Results: Eleven (1.7%) of 632 scrub typhus patients were diagnosed with ARDS (median age 72; seven were male). Eight patients had underlying diseases, the most common of which was hypertension (four patients). Eight patients (72.7%) were admitted in November. The most common chief complaints of the patients were fever and rash (63.6%). All patients had skin eschar and rash; seven were treated for shock. On the day of diagnosis with ARDS, the median Acute Physiology and Chronic Health Evaluation score was 20 (range 11-28) and Sequential Organ Failure Assessment score was 7 (range 4-14). All patients had PaO_2/FiO_2 < 200 mmHg, high serum aspartate aminotransferase level (> 40 IU/L), and hypoalbuminemia (< 3.3 g/dl). Nine patients were treated with doxycycline on the day of admission. Their median lengths of stay in the ICU and hospital were 10 (range 4-65) and 14 (4-136) days, respectively. The mortality rate during treatment in the hospital was 36.4%.
Conclusions: In our study, the risk of ARDS among patients diagnosed with scrub typhus was at least 1.7%, with a hospital mortality rate of 36.4%.

Key Words: acute respiratory distress syndrome; intensive care unit; scrub typhus.

Introduction

Scrub typhus is a mite-borne infectious disease caused by *Orientia tsutsugamushi*[1] distributed throughout the Asia–Pacific area.[2] Scrub typhus, an acute febrile disease, is characterized by a typical primary necrotic lesion (eschar), generalized lymphadenopathy, rash, and non-specific symptoms such as fever, headache, myalgia and cough. Rarely, severe complications, including prominent encephalitis, interstitial pneumonia, acute respiratory distress syndrome (ARDS), acute renal and hepatic failure, and acute hearing loss, have been reported.[3-8] Serious pulmonary involvement such as ARDS has rarely been seen, likely because of the introduction of specific antibiotic therapy. Although one observational study reported the clinical characteristics of eight patients with ARDS,[9] scrub typhus complicated by ARDS has seldom been discussed; few case reports have been published.[10-13] Moreover, no reports include data on the clinical characteristics of these patients in South Korea.

The aim of this study was to investigate the clinical course and outcome of patients diagnosed with ARDS caused by scrub typhus and received ventilator care in the intensive care units (ICU)

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of two university hospitals in Busan, South Korea. Also, we examined potential differences from previous reports.[9]

Materials and Methods

1) Study subjects

We performed a retrospective search of all adult patients (age ≥ 17 years) admitted to the ICU who met the criteria for both code A753 (scrub typhus) and J80 (ARDS) according to the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10). A total of 11 ventilated patients diagnosed with ARDS caused by scrub typhus were enrolled in this study. Of these patients, nine were from Pusan National University Hospital between 1 January 1995 and 31 December 2012 and two were from Haeundae Baik Hospital between 1 January 2010 and 31 December 2012. ARDS patients were managed according to the therapeutic guideline for lung-protective ventilation.[14] Medical records and laboratory and radiographic findings of all patients were collected. Investigators from each center completed a case report form, and data were collected from September to October 2013. Three investigators (SYK, KS and KL) confirmed that the study objectives and procedures were honestly disclosed, and both had full access to all of the data. The protocol for this study was approved by the Institutional Review Boards of the two participating institutions.

2) Data collection

The following data were gathered from the medical records of each patient: age, gender, duration of mechanical ventilation, length of stay in the ICU and in the hospital, hospital mortality, month of admission and chief complaint at admission. Acute Physiology and Chronic Health Evaluation (APACHE) and Sequential Organ Failure Assessment (SOFA) scores were calculated on the day of ARDS diagnosis.[15,16] The Charlson Comorbidity Index was calculated from medical records.[17] The following laboratory data collected on the day of ARDS diagnosis were obtained from medical records: white blood cell count, lowest PaO_2/FiO_2 ratio, C-reactive protein, blood urea nitrogen (BUN), creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, and albumin level. In addition, we recorded the occurrence of septic shock at ARDS diagnosis, tracheostomy during hospitalization, and time from admission to the beginning of treatment with doxycycline.

3) Definition

A diagnosis of scrub typhus was based on an indirect microimmunofluorescence antibody (IFA) test for *O. tsutsugamushi*. Diagnostic IFA results were positive if total antibody titer showed a fourfold increase in paired positive serum samples or the antibody titer was ≥ 1:160.[18,19] The diagnosis of ARDS was based on the consensus criteria of the American-European Consensus Conferences, which was defined as acute onset, $PaO_2/FiO_2 \leq 200$ mmHg regardless of positive end-expiratory pressure, bilateral infiltrates seen on frontal chest radiograph, and pulmonary artery wedge ≤ 18 mmHg when measured or no clinical evidence of left atrial hypertension.[20] Sepsis, severe sepsis, and septic shock were defined using criteria from the American College of Chest Physicians/Society of Critical Care Medicine.[21] Acute kidney injury was defined as oliguria and marked increase in BUN and creatinine, and ventilator-associated pneumonia was defined as a modified Clinical Pulmonary Infection Score of 6 or greater.[22] Survivors were defined as patients who survived to discharge from hospital.

4) Statistical analysis

Continuous variables are expressed as medians and ranges and compared using the Mann-Whitney U-test. Categorical variables were compared using chi-square and Fisher's exact tests. All statistical analyses were performed using the Statistical Package for the Social Sciences (version 18.0, SPSS, Chicago, IL, USA). A two-tailed $p < 0.05$ was considered to indicate statistical significance.

Results

During enrolled period, a total of 632 patients were diagnosed with scrub typhus. Of these patients, eleven were diagnosed with ARDS. Patients' characteristics and their clinical courses are summarized in Table 1. The median patient age was 72 (range 29-85) years, and seven (63.6%) patients were male. Eight patients (72.7%) had underlying diseases and most common underlying disease was hypertension (four patients). The median Charlson Comorbidity Score was 1 (range 0-3). Eight patients (72.7%) were admitted in November. The most common chief complaint of the patients was fever and dyspnea (63.6%). All patients had skin rash and eschar; seven were also treated for shock. The median APACHE and SOFA score on the day of diagnosis with ARDS were 20 (range 11-28) and 7 (4-14), respectively. All patients had $PaO_2/FiO_2 < 200$ mmHg, high serum AST levels (> 40 IU/L), and hypoalbuminemia (< 3.3 g/dl). Seven patients had

Table 1. Characteristics and clinical courses of eleven scrub typhus patients with acute respiratory distress syndrome

N	Age/ Sex	Month of admission	Chief complaint	APACHE II score	SOFA score	CCI	MV LOS	ICU LOS	Hospital LOS	Shock	PaO_2/FiO_2 (mmHg)	Complication during hospital course	Hospital outcome
1	77/M	November	RUQ pain, fever	23	11	2	17	20	26	Yes	66.6	Pneumonia	Survived
2	72/M	December	Dyspnea, fever	15	6	1	6	7	13	Yes	70.5	None	Survived
3	72/M	October	Fever	23	6	3	1	10	19	No	155.2	None	Survived
4	83/F	November	Fever	17	7	0	5	9	18	No	106.6	None	Survived
5	66/M	November	Dyspnea, fever	22	5	0	6	6	13	No	101.8	None	Survived
6	64/M	November	Dyspnea, fever	25	11	1	61	65	136	Yes	107.5	Pneumonia, TEN	Survived
7	85/M	November	Hematochezia	18	10	1	1	14	14	No	73.5	Ischemic colitis	Died
8	67/F	November	Dyspnea, fever	15	9	1	12	12	12	Yes	114.1	None	Died
9	73/M	November	Dyspnea	28	14	1	4	4	4	Yes	41.8	Acute kidney injury, encephalitis	Died
10	66/F	November	Dyspnea	20	4	3	18	19	20	Yes	88.0	Acute kidney injury	Died
11	29/F	October	Dyspnea	11	5	0	5	5	13	Yes	53.0	None	Survived

APACHE: acute physiology and chronic health evaluation; SOFA: sequential organ failure assessment; CCI: charlson comorbidity index; MV: mechanical ventilation; ICU: intensive care unit; LOS: length of stay; RUQ: right upper quadrant; TEN: toxic epidermal necrolysis.

diagnostic IFA results, which all patients had the antibody titer was ≥ 1:160. Nine patients were treated with doxycycline on the day of admission (range of interval from hospital admission to commencement of antibiotic, 0-5). The two most common complications in the study population were hospital-acquired pneumonia and acute kidney injury (each occurring in 2 of 11 or 18.2% of patients). The median duration of ventilator care was 6 days (range 1-61), and median length of stay in the ICU and hospital were 10 (range 4-65) and 14 (4-136) days, respectively. One patient was received tracheostomy. The hospital mortality rate was 36.4% (4 of 11). However, there were no significant differences regarding the above clinical characteristics and laboratory data between survivors and non-survivors (data not shown).

Discussion

This study investigated the clinical characteristics of patients with ARDS caused by scrub typhus in South Korea. According to the literature, the pulmonary manifestations of scrub typhus are varying grades of bronchitis and interstitial pneumonitis progressing to ARDS.[23] ARDS might arise as a result of the immunological response of the lung to previous *O. tsutsugamushi* infection without direct invasion of the organism.[9,10] Also, interstitial pneumonia might be associated with disease severity as reported in a previous study.[24]

In the present study, we found that all patients had low comorbidity scores, and most patients were hospitalized in November. These findings suggest that development of ARDS caused by scrub typhus does not correlate with underlying diseases and that November might be a period during which development of ARDS is prevalent.

Also, the five major clinical symptoms are well known to include fever, headache, eschar, rash, and lymphadenopathy; 83% of the cases presented with one to three clinical symptoms and 10% with four to five symptoms.[25] However, in this study, the chief complaint was dyspnea and fever, which was consistent with a previous report;[9] initial respiratory symptoms at the time of diagnosis with scrub typhus might be an indication for careful evaluation for progression to ARDS.

Several published case reports and study described clinical manifestations in patients with ARDS caused by scrub typhus which are summarized in Table 2.[9-13] Compared with these previous reports, all our patients presented with hypoalbuminemia, which was consistent with previous reports.[9,11-13] In the reported data in Taiwan, hypoalbuminemia was an independent predictor for development of ARDS. Though we hypothesized this feature would also indicate prognosis in our patients, the small sample size prevented a clear conclusion.

Treatment with doxycycline usually lowers fever within 24 hours, and severe complications such as sepsis and ARDS are typically the result of delayed diagnosis and treatment. In our study, all patients were treated with doxycycline, and 10 patients (91%) received antibiotics within 2 days after hospitalization. This interval was somewhat shorter than in a previous report[9] (median: 0 vs. 8 days). However, the mortality rate we observed was higher than in that study.[9] This difference may be due to the fact that all patients included in our analysis had low PaO_2/FiO_2, and 63.6% were experiencing shock at ARDS diagnosis. Our results suggest that the mortality rate in patients with ARDS caused by scrub typhus is higher than that for scrub typhus overall, even with prompt treatment using appropriate antibiotics.

Table 2. Summary of previous case reports and study of patients with acute respiratory distress syndrome caused by scrub typhus

	Age/ Sex	Chief complaint	MV LOS	Hospital LOS	PaO_2/FiO_2 (mmHg)	WBC (/mm^3)	CRP (mg/dl)	AST (IU/L)	ALT (IU/L)	Total bilirubin (mg/dl)	Albumin (g/dl)	Creatinine (mg/dl)	Hospital outcome
Park et al.[10] (Korea, case report)	72/F	Dyspnea	10	15	161.2	14,000	0.89	Unknown	Unknown	Unknown	Unknown	Unknown	Died
Kurup et al.[11] (Singapore, case report)	35/M	Fever	7	11	Unknown	12,300	18.2	113	140	0.22	2.4	1.54	Survived
Tseng et al.[12] (Taiwan, case report)	67/M	Dyspnea	Unknown	Unknown	51.1	10,800	14.0	63	93	0.5	2.3	0.8	Survived
Ryu et al.[13] (Korea, case)	78/M	Decreased mental status	87	Unknown	Unknown	9,450	19.0	57	43	0.85	1.78	1.71	Survived
Wang et al.*[9] (Taiwan, 8 patients)	Age: 55.3 ± 21.5 M/F: 3/5	Fever, cough (100%) Dyspnea (87.5%)	14.8 ± 10.4	Unknown	Unknown	11,330 ± 4,660		148.3 ± 81.8	133.7 ± 78.0	3.5 ± 3.4	2.2 ± 0.4	1.0 ± 0.4	Mortality : 25%
This study* (Korea, 11 patients)	Age: 68.6 ± 14.8 M/F:7/4	Fever, dyspnea (63.6%)	12.4 ± 17.1	26.2 ± 36.9	89.0 ± 32.3	12,022 ± 4,597	17.3 ± 10.0	111.2 ± 72.3	66.0 ± 39.7	1.4 ± 1.4	2.1 ± 0.4	1.1 ± 0.5	Mortality : 36%

*All data are presented as mean ± SD. MV: mechanical ventilation; LOS: length of stay; WBC: white blood cell; CRP: C-reactive protein; AST: aspartate aminotransferase; ALT: alanine aminotransferase.

There were several limitations to our research because of its retrospective design and the small number of patients. First, we hypothesized that all patients would have serious neurologic complications caused by scrub typhus at admission; because a previous study showed that the presence of pneumonitis was associated with the occurrence of scrub typhus meningitis and meningoencephalitis.[26] However, we could not identify additional complications as shown in Table 1 because the study was retrospective. Second, there would be different serotype of *Orientia tsutsugamushi* depending on the region, which might be associated with different disease severity and clinical outcome. Therefore, our study reflected the regional characteristics, especially focused on Busan area.

In conclusion, our study found the risk of ARDS among patients diagnosed with scrub typhus was at least 1.7%, and their hospital mortality rate was 36.4%. Further, large-scale studies are needed to identify prognostic indicators for development of ARDS and to establish whether the clinical outcomes of scrub typhus differ according to the respiratory reaction.

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