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Acute Cholecystitis in Patients with Scrub Typhus

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Acute cholecystitis is a rare complication of scrub typhus. Although a few such cases have been reported in patients with scrub typhus, the clinical course is not well described. Of 12 patients, acute cholecystitis developed in 66.7% (8/12) of patients older than 60 yr. The scrub typhus group with acute cholecystitis had marginal significant longer hospital stay and higher cost than the group without cholecystitis according to propensity score matching. Scrub typhus should be kept in mind as a rare etiology of acute cholecystitis in endemic areas because the typical signs of scrub typhus such as skin rash and eschar can present after the abdominal pain.

Keywords: Cholecystitis; Acute; Scrub Typhus; Complication; Propensity Score

Scrub typhus is an acute febrile disease caused by *Orientia tsutsugamushi*, which is characterized by high fever, maculopapular skin rash, lymphadenopathy, headache, myalgia, and eschar (1). The symptoms of this disease are usually mild and self-limited; however, it is sometimes accompanied by severe complications such as pneumonia, acute kidney injury (AKI), acute respiratory distress syndrome (ARDS), meningoencephalitis, shock, gastrointestinal bleeding, and myocarditis (2-8). Scrub typhus complicated by acute cholecystitis has been rarely reported, and the clinical course of this complication is not well understood (9-14). Herein, we conducted a retrospective study to investigate the characteristics of acute cholecystitis in patients with scrub typhus. We found 12 cases of scrub typhus complicated by acute cholecystitis and described it with literature review. Additionally, comparison between scrub typhus patients with and without acute cholecystitis was performed using propensity score matching.

The study was approved and performed according to the guidelines of the institutional review board of Chonbuk National University Hospital (IRB Number: CUH 2013-10-014). Informed consent was waived due to the retrospective nature of the study. Medical records of subjects who were diagnosed with scrub typhus were evaluated from January 2005 to December 2012 in Chonbuk National University Hospital. Those patients whose course was complicated by acute cholecystitis were selected and enrolled in this study. Data collection was also conducted from the following electronic databases: PubMed and website of The Korean Journal of Internal Medicine (http://www.kaim.or.kr/journal/searchlist.php), including reports up to August 2013. The following words were used for searching: "scrub typhus" or "tsutsugamushi". Thereafter, cases that described acute cholecystitis as a complication of scrub typhus were assessed. Two researchers searched the electronic database and collected cases independently using the same searching protocols. We also checked the references from the retrieved papers to ensure we did not miss any additional cases. When data (e.g. total dates of hospitalization and the onset of symptoms before admission) were ambiguous, we contacted the authors of the selected articles for clarification. Data from only fully published papers were included, and those from conferences and abstracts were excluded.

The diagnosis of five patients with scrub typhus in this hospital was confirmed by positive IgM titer ≥ 1:160 against *O. tsutsugamushi* or a fourfold or greater rise in the indirect immunofluorescence assay (IFA, Green Cross Reference Lab., Yongin, Korea). Acute cholecystitis in these patients was diagnosed according to updated Tokyo Guidelines 2013 (15). Appropriate antibiotics included doxycycline and azithromycin for treatment

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of these patients.

The diagnosis of scrub typhus in the electronic database was confirmed by positive IgM titer ≥ 1:80 against *O. tsutsugamushi* or a fourfold or greater rise in the indirect immunofluorescence assay. The diagnosis of acute cholecystitis was confirmed when the clinical parameters described in the electronic data met the diagnostic criteria of the updated Tokyo Guidelines 2013. Appropriate antibiotics for the electronic data included minocycline, doxycycline, or azithromycin (16).

The Mann-Whitney *U* test and Fisher's exact test were used for continuous and categorical variables. For propensity score matching, cases with malignancy, liver cirrhosis, acute renal failure, chronic renal failure, severe pulmonary disease, and other immunosuppressive status were excluded. Thereafter, we matched cases and controls using propensity score matching methods of logistic regression (propensity score was calculated by using age, gender, hypertension, and diabetes mellitus) and nearest neighbor matching (matching one to three). All analysis was performed using SPSS R extension (IBM SPSS Statistics for Windows, Version 21.0 and R packages [R 2.14.2]), and *P* values less than 0.05 were considered significant.

We identified 442 patients who satisfied diagnostic criteria for scrub typhus. Among them, a total of 5 patients (1.1%) were identified to have both acute cholecystitis and scrub typhus. A total of 1,733 reports were searched in PubMed (n = 1,710) and website of The Korean Journal of Internal Medicine (n = 23). A total of 7 subjects were identified as having scrub typhus complicated by acute cholecystitis (9-14).

Of 12 patients, 4 (33.3%) were male, and the median age was 73.0 yr (interquartile range [IQR], 52.8-80.3 yr). Epigastric or right upper quadrant abdominal pain and RUQ tenderness or Murphy's sign were present in all patients. Acute cholecystitis developed in 66.7% (8/12) of patients older than 60 yr. There were no deaths due to scrub typhus complicated by acute cholecystitis, although two patients were referred to local hospitals after withdrawal of care. Leukocytosis (> 10,000/μL), elevated creatinine (> 1.4 mg/dL), and low albumin (< 3.0 g/dL) were found in 33.3% (4/12), 10.0% (1/10), and 33.3% (3/9), respectively. Gallbladder stones or sludge were present in 33.3% (4/12). Of 12 patients, five patients (41.7%) were diagnosed with acute cholecystitis before the clinical diagnosis or suspicion of scrub typhus, which resulted in delayed treatment of scrub typhus. Procedures such as percutaneous transhepatic gallbladder drainage or emergent operations were performed in 41.7% (5/12). One or more complications other than acute cholecystitis, such as pneumonia, AKI, shock, disseminated intravascular coagulopathy (DIC), and ARDS occurred in 83.3% (10/12).

The median length of hospitalization of 12 patients was 18.5 days (Table 1, IQR, 14.5-28.3 days). The median length of hospitalization in the five patients who started proper antibiotics within 6 days after the onset of symptoms was 14.0 days (IQR, 9.5-18.0 days). In contrast, the median length of hospitalization in the six patients who started proper antibiotics more than seven days after the onset of symptoms was 22.5 days (IQR, 17.8-30.3 days).

A comparison of the clinical characteristics of scrub typhus patients with and without cholecystitis according to propensity score matching was performed to compare hospital duration and cost. The scrub typhus group with acute cholecystitis had marginally significantly longer hospital duration and higher cost than the group without cholecystitis (Table 1, $P = 0.053$, $P = 0.053$).

Many complications have been reported in patients with scrub typhus including pneumonia, AKI, ARDS, meningoencephalitis, shock, and myocarditis (2-8). The development of these complications is associated with prolonged hospitalization and higher medical costs (17). We showed that early diagnosis and treatment with proper antibiotics are very important because the length of hospitalization was shorter in patients treated with proper antibiotics within seven days. In the previous study, the mean length of hospitalization in patients with severe scrub typhus was 11.5 ± 9.6 days compared to 7.21 ± 2.8 days in patients with non-severe scrub typhus (11). Furthermore, it can be assumed that higher medical costs might be paid in patients with acute cholecystitis due to additional imaging studies, use of various antibiotics, and longer hospital days. In our study, the length of hospitalization and the medical cost for treating scrub typhus patients complicated by acute cholecystitis were marginally significantly higher than patients without acute cholecystitis.

Although the mechanism of development of acute cholecystitis in scrub typhus is largely unknown, it has been suggested that systemic vasculitis or perivasculitis caused by *O. tsutsuga-*

Table 1. Characteristics of scrub typhus patients with and without cholecystitis according to propensity score 1 to 3 matching

Parameters		Scrub typhus with cholecystitis (n = 5)	Scrub typhus without cholecystitis (n = 15)	*P* value*
Age (yr)		81.0 (76.0-84.0)	81.0 (78.0-84.0)	0.800
DM	Yes	1 (20.0)	5 (33.3)	1.000
	No	4 (80.0)	10 (66.7)	
HTN	Yes	3 (60.0)	8 (53.3)	1.000
	No	2 (40.0)	7 (46.7)	
Length of hospitalization (day)		26 (9.5-104.5)	8 (3-15)	0.053
Hospital cost† (USD)		7,361.37 (3,834.38-32,880.53)	2,963.60 (1,043.41-7,212.55)	0.053

Data were presented by median (interquartile range) or number (percentage). *Analyzed by Mann-Whitney *U* test (age, hospital duration, and hospital cost) or Fisher's exact test (Gender, DM, and HTN); †Hospital cost (Korean won) was converted to United States dollars according to the 8/18/2014 exchange rate. DM, diabetes mellitus; HTN, hypertension.

mushi is a likely cause, similar to other complications (10). Traditionally, old age (> 60 yr), male gender, and the presence of cardiovascular disease and diabetes mellitus have been regarded as risk factors for acute calculous cholecystitis (18). In contrast severe illness causing ischemia of the gall bladder is a risk factor for acute acalculous cholecystitis (9,19). As for scrub typhus, old age (> 60 yr), elevated creatinine (> 1.4 mg/dL), low albumin (< 3.0 g/dL), and leukocytosis (WBC > 10,000/μL) have been shown to be associated with the development of various complications in scrub typhus (6,17). In our study, old age (> 60 yr) was observed in 66.7% (8/12) of patients with scrub typhus complicated by acute cholecystitis, suggesting an association between old age and the development of acute cholecystitis. Although no deaths were reported, various complications were observed in most cases.

There are several limitations to the present study. First, it was conducted retrospectively at a single referral center in an area with a high prevalence of Boryong serotype. Therefore, our study may not be applicable to other regions due to geographic differences. Second, the number of patients was relatively small to confirm our conclusion, although our study suggested that early diagnosis and medical treatment with appropriate antibiotics are important in scrub typhus patients with acute cholecystitis.

In conclusion, we suggest that acute cholecystitis be considered in patients with scrub typhus who develop epigastric or RUQ pain. Additionally, scrub typhus should be kept in mind as a rare etiology of acute cholecystitis in endemic areas and seasons because the typical signs of scrub typhus such as skin rash and eschar can present after the abdominal pain or can even be absent as shown in some cases.

DISCLOSURE

The authors have no conflicts of interest to disclose.

AUTHOR CONTRIBUTION

Study conception and design: Lee H, Ji M, Hwang JH, Chung KM, Lee CS. Clinical and laboratory data collection: Lee H, Ji M, Lee JY, Hwang JH. Data analysis and drafting: Lee JH, Chung KM, Lee CS. Revision and approval of manuscript submission: all authors.

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