

## Case Report



# Acute Cholangitis Caused by Boryong Strain of *Orientia tsutsugamushi*

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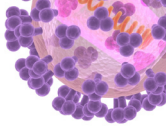
## ABSTRACT

Scrub typhus present with a variety clinical manifestations caused by *Orientia tsutsugamushi*, it is sometimes accompanied by severe complications. The clinical course of this complication is not well clear. Herein, we first report a case with acute cholangitis and acalculous cholecystitis caused by the Boryong genotype of *O. tsutsugamushi*. A 82-year-old woman presented with fever and acute abdominal pain on the right upper quadrant. Initially, the patient showed an abnormality of liver enzymes of cholestatic pattern. An acute cholangitis and cholecystitis were suspected on the enhanced computed tomography (CT), and emergent endoscopic retrograde cholangiopancreatography (ERCP) performed. However, neither ERCP nor CT detected common bile duct stones or sludge. The patient's illness progressed despite bile drainage and antibiotic therapy. On the fifth day in hospital, an immunofluorescence IgG assay for *O. tsutsugamushi* was positive, and the patient newly developed a skin rash and an eschar lesion on the right abdomen. The polymerase chain reaction amplification of *Orientia* genes from blood and bile was positive, genotype of both samples was identified the Boryong type. The presentation of scrub typhus as an acute cholangitis is not reported till now. In endemic areas, scrub typhus would be considered a rare etiology of acute cholangitis.

**Keywords:** Tsutsugamushi Disease; *Orientia tsutsugamushi*; Cholangitis


## INTRODUCTION

The clinical manifestations of scrub typhus vary and are accompanied by severe complications caused by injuries to multiple organs [1]. However, an acute cholecystitis and cholestatic hepatitis are a rare complication of scrub typhus [2-4], and acute cholangitis has not been previously reported as a complication. Although the mechanism of the development of acute cholecystitis and hepatitis consequent to scrub typhus is unknown, systemic vasculitis or perivasculitis caused by *Orientia tsutsugamushi* has been suggested [5]. Herein, we report the first case where in the patient had no typical symptoms or signs of scrub typhus at the time of visit but was found to have acute cholangitis and acalculous cholecystitis caused by the Boryong genotype of *O. tsutsugamushi* and present this novel case in the context of a literature review.



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**Conflict of Interest**

No conflicts of interest.

**Author Contributions**

Conceptualization: JRY. Data curation: KHL.

Formal analysis: STH, SUJ, MK. Investigation:

KHL, WSJ. Methodology: YKK. Resources:

CLH. Validation: KHL. Writing - original draft:

KHL, STH, SUJ. Writing - review & editing: JRY.

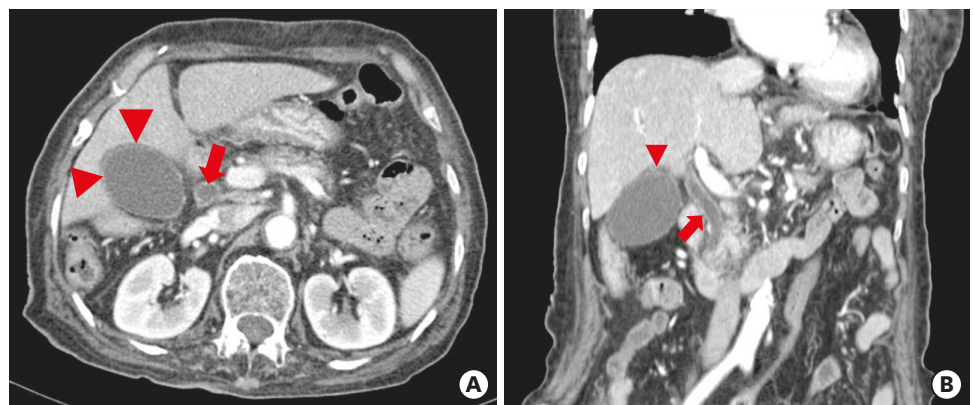
**CASE REPORT**

A 82-year-old woman presented with a 4-day history of fever, general weakness, and postprandial abdominal distension and 3-day history of nausea and vomiting. At the time of admission, she had abruptly developed an altered mental status and acute abdominal pain in the right upper quadrant. Her history was unremarkable, except that she reported removing weeds from a garden one week earlier, during autumn. She was unaware of receiving an insect bite.

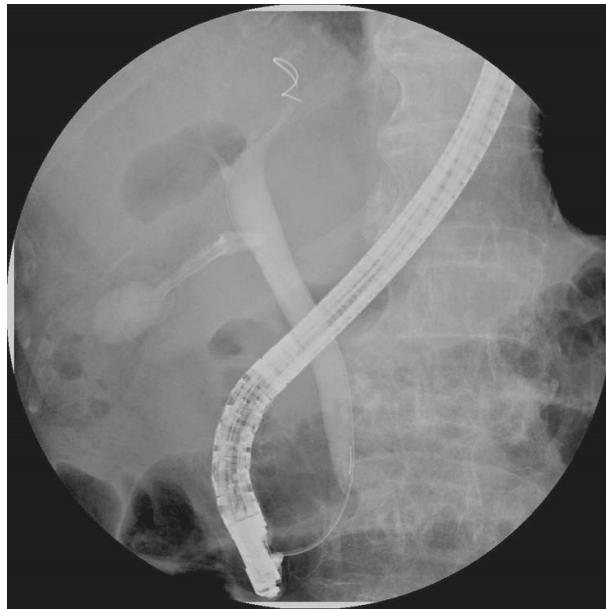
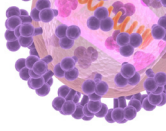
The patient's laboratory examination revealed leukocytosis, with a white blood cell count of 14,400/mm<sup>3</sup>. Additionally, increased levels of alkaline phosphatase (1,410 U/L), aspartate aminotransferase (248 IU/L), alanine aminotransferase (205 IU/L), alkaline phosphatase (1,410 U/L), and  $\gamma$ -glutamyl transpeptidase (222 U/L) were detected. A contrast-enhanced computed tomography (CT) scan revealed wall enhancement of the dilated common bile duct (CBD) and a dilated gallbladder (GB) with pericholecystic fluid collection (**Fig. 1A and 1B**, red arrowhead). Acute cholangitis and cholecystitis were suspected, and an emergent endoscopic retrograde cholangiopancreatogram (ERCP) with nasobiliary drainage was performed on the second hospital days. However, neither ERCP nor CT detected CBD stones or sludge (**Fig. 2**).

On the fourth hospital days, the patient's illness progressed despite bile drainage and antibiotic therapy. Accordingly, she underwent an urgent cholecystectomy for acute cholecystitis on the fifth day in hospital. Although the surgical specimen revealed a grossly normal GB and CBD, the pathological analysis revealed active inflammation with focal atrophic and ischemic changes under the mucosal epithelium (**Fig. 3A and 3B**). On the fifth hospital days, an immunofluorescence IgG assay for *O. tsutsugamushi* was positive (titer 1:1,280), and the patient newly developed a multiple popular rash and a necrotic eschar lesion on the right abdomen (**Fig. 4**). This rash and eschar was not showed at the emergency department and on the second hospital days. Bile and blood cultures conducted using the Bact/Alert 3D system (bioMérieux Inc., Marcy-l'Etoile, France) showed no growth.

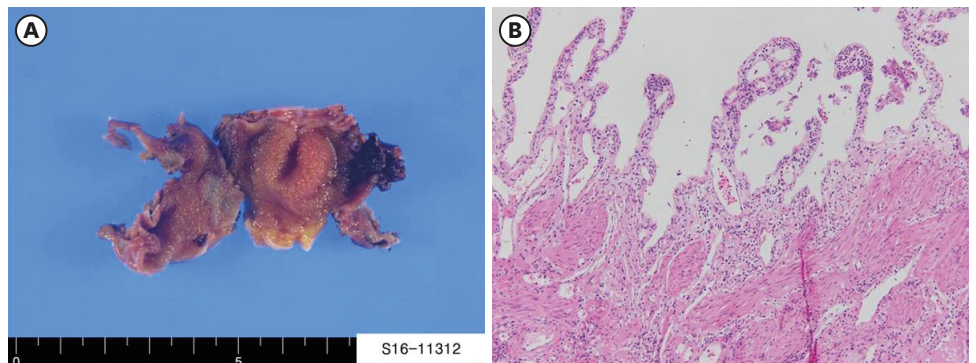
Although the patient did not recall being bitten by a tick, we extracted DNA from stored samples of the patient's serum and bile using a QIAamp DNA Mini Kit (QIAGEN, Hilden, Germany) and performed nested PCR to amplify the 56-kDa antigen of *O. tsutsugamushi*. The results confirmed the *O. tsutsugamushi* infection. The nested-PCR product (483 bp) was clone-sequenced using the BigDye Terminator Cycle Sequencing kit (Perkin-Elmer



**Figure 1.** A contrast enhanced computed tomography scan revealed a wall enhancement of the dilated common bile duct (red arrow), and also revealed a dilated gallbladder with pericholecystic fluid collection (red arrowhead).



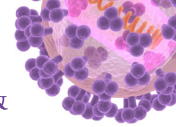
**Figure 2.** There was no common bile duct stone or sludge on endoscopic retrograde cholangiopancreatogram.



**Figure 3.** (A) A gross inspection of gall bladder. (B) A gall bladder biopsy showed an active inflammation with focal atrophic and ischemic change under the mucosal epithelium (hematoxylin and eosin  $\times 100$ ).



**Figure 4.** She showed an eschar lesion (0.7 cm x 0.4 cm) on the right upper quadrant which it was covered with right breast.



Applied Biosystems, Warrington, UK), and a Basic Local Alignment Search Tool (BLAST) analysis revealed a close relationship with *O. tsutsugamushi* (98% homology). A subsequent phylogenetic analysis grouped the sequence with the Boryong strain. Doxycycline treatment was initiated, and the patient's overall illness improved after 14 days. The study protocol was approved by the Institutional Review Board of Jeju National University Hospital (JNUH 201511001) and informed consent was obtained from participant.

## DISCUSSION

To our knowledge, this is the first case of acute cholangitis caused by the Boryong strain of *O. tsutsugamushi*. The clinical features of Rickettsial infections are non-specific, and many common febrile illnesses can mimic Rickettsioses [6]. Additionally, scrub typhus rarely manifests as acute abdomen. The patient in this case did not present with a rash and typical eschar at the time of hospital admission and underwent emergent treatment for common acute acalculus cholangitis and cholecystitis. In previous reports of scrub typhus with acute cholecystitis, most patients presented with upper abdominal pain, changes in aminotransferase levels, and wall enhancement and distension of the GB on CT, leading to suspicions of acute cholecystitis and considerations of surgical treatment. As these patients did not present with a typical eschar [2, 3, 5, 7], physicians did not include scrub typhus in the differential diagnosis of cholecystitis.

We consider our case to be interesting for the following reasons. First, we identified *O. tsutsugamushi* from the patient's bile and blood specimens. *O. tsutsugamushi* targets endothelial cells and macrophages and disseminates into multiple organs; in severe cases, this can lead to pneumonitis, encephalitis, cholestatic hepatitis, and myocarditis [2]. The endothelial cell destruction and perivascular leukocyte infiltration associated with scrub typhus causes disseminated multi-organ vasculitis and perivasculitis of the small vessels [8, 9]. The mechanism responsible for the development of acute cholecystitis and nonspecific hepatitis may also be related to vasculitis [4, 10-12]. However, we could not determine whether the acute cholangitis in the present case was non-specific or attributable to a primary *O. tsutsugamushi* infection. However, the right upper quadrant pain, wall enhancement of the CBD, and identification of *O. tsutsugamushi* from bile suggest that the patient's condition arose from a primary *O. tsutsugamushi* infection. Currently, the mechanism by which scrub typhus causes this complication remains largely unknown. Future studies should assess certain monoclonal and polyclonal antibodies against prototypic strains of *O. tsutsugamushi* and conduct molecular testing for *Orientia* species from involved organs to confirm our preliminary findings. Second, the patient did not initially present with an eschar and rash characteristic of scrub typhus. As the symptoms typically include a fever and maculopapular rash, the diagnosis of scrub typhus often relies on the presence of a typical painless necrotic eschar. However, a previous study found that the mean overall incidence of eschar in cases of Rickettsial disease (RD) was only 64.3%, and therefore 66.5% of all patients were misdiagnosed [13]. In Korea, the incidence rates of eschar and rash among confirmed cases of scrub typhus were 78.9% and 46.8%, respectively [14]. The incubation period of scrub typhus is usually 6 - 21 days, followed by the development of fever, eschar, and rash. Rash is generally observed 3 - 7 days after onset and is evident in only 14% of patients on the first day of illness and 49% during the first 3 days. Similarly, necrotic eschar is typically observed during the first 4 - 7 days of illness [15, 16]. As the patient arrived at the hospital within 3 days of symptom onset, the characteristic skin lesions may not have yet emerged.

In conclusion, it is very difficult to differentiate clinically between obstructive acute cholangitis and scrub typhus caused by a biliary tract infection. In endemic areas, scrub typhus would be considered a rare etiology of acute cholangitis and could be easily treated with antibiotic therapy. Furthermore, in these areas and during endemic seasons, physicians should consider the possibility of an acute biliary tract infection caused by *O. tsutsugamushi* in cases of nonspecific acute cholangitis.

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