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Case Report

Coxiella burnetii infection in a patient with tick bite

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Abstract

Introduction: We report the case of a 60-year-old male who was hospitalized with fever, headache, fatigue, nausea, and myalgia for six days.
Methodology: Polymerase chain reactions (PCR) were performed on patient blood samples, and four ticks were collected from the area the patient mowed. Indirect immunofluorescence assays (IFAs) were performed on serum samples to detect specific antibodies.
Results: The collected ticks were identified as *Haemaphysalis longicornis*. *Coxiella* species-specific nested PCR (N-PCR) and sequencing confirmed the presence of *Coxiella burnetii* in the patient, and *Coxiella*-like bacteria were identified in three of the four ticks. IFA results showed ≥ 4-fold increases in both IgM and IgG antibody titers against Q fever.
Conclusions: Despite positive PCR results for *Coxiella* species in both the patient and the ticks, different bacterial species were isolated, suggesting that the patient was not infected with *C. burnetii* through tick bites. Further investigation is required to identify the carriers or transmitters of the infection.

Key words: *Coxiella burnetii*; Q fever; tick; polymerase chain reaction; immunofluorescence assay.

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Introduction

Coxiella burnetii, a Gram-negative bacterium that causes Q fever, is highly infectious and can survive in stressful environments for several weeks [1]. Various wild animals, birds, amphibians, arthropods, and livestock, can also carry *C. burnetii* [2].

The main routes of transmission are contaminated aerosols or consumption of raw milk from infected animals [3]. Other routes of transmission are minor or controversial [4]. Human infections are thus commonly associated with direct contact with animal reservoirs. People working in slaughterhouses, timber industry, agricultural farms, and veterinary practices are at elevated risk of *C. burnetii* infection [5].

The best diagnostic tool is *C. burnetii* isolation. However, isolation is time consuming, hazardous, and requires a biosafety level 3 facility. Polymerase chain reaction (PCR) and indirect immunofluorescence assays (IFA) are currently the clinically preferred diagnostic tools [6]. If ticks are found on a patient, the causative agent can be detected by PCR amplification of the tick hemolymph [7]. The role of ticks in the maintenance and transmission of *C. burnetii* remains controversial, and no xenodiagnostic assay has demonstrated a relevant role to date. Many studies have attempted to identify a relationship between tick bites and *C. burnetii* infection in humans. For example, Eklund *et al*. reported a case of a human *C. burnetii* infection that might have involved contact with ticks in a natural setting [8]. However, these authors did not investigate the presence of this bacterium in ticks.

Sequencing and phylogenetic analyses are necessary for the precise identification of *C. burnetii* [9]. The present case involves a patient with Q fever. We explored whether tick bites were involved in transmission using PCR, a phylogenetic tree, and IFA.

Case Report

On April 22, 2018, a 60-year-old man was hospitalized with fever. His vital signs were as follows: blood pressure was 140/90 mm Hg, heart rate was 88 beats per minute, respiratory rate was 18 times per minute, and temperature was 39.2 °C. The patient had no underlying diseases. While recording his history, it was revealed that he had been mowing for three days, 13 days prior to hospitalization, and had manifested

symptoms including headache, fatigue, nausea, and myalgia for six days before hospitalization.

Upon admission, hematological and biochemical examinations revealed normal results. However, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were higher than the normal range at 144/183 IU/L (reference range: 5–40/5–40 IU/L), but prothrombin time, total bilirubin, and C-reactive protein levels were within the normal range. PCR and antibody tests were performed by following the manufacture's instruction to detect influenza A/B, *Leptospira*, Hantavirus, and *Orientia tsutsugamushi*. None of these pathogens were detected. Blood was cultured, and no bacterial growth was detected. After hospitalization, the patient reported that he had found ticks on his body and clothes while showering, although he could not recall the moment he was bitten. We thus collected ticks from the mowing location.

The life cycle stages and species of the ticks were morphologically classified using microscopy and standard taxonomic keys. Genomic DNA was extracted from a 300 μL blood sample from the patient, and from each ground tick lysate (150 μL). Nested-PCR (N-PCR) and real-time PCR were performed to diagnose Q fever, rickettsial disease, Lyme disease, and anaplasmosis in blood specimens and in the four ticks. The *htpAB*-associated repetitive element (IS1111) and 16S ribosomal RNA (*16S rRNA*) genes were targeted to detect *Coxiella* sp. [10,11].

In order to detect the presence of rickettsia DNA, the outer membrane protein A gene (*ompA*) of the spotted fever group *Rickettsia* species and the 23S rRNA gene of *Rickettsia* (panrickettsia) were targeted [12-14]. The CTP synthase (*pyrG*) gene was targeted to detect *Borrelia* species [15]. The heat shock protein gene (*groEL*) and the ankyrin-related protein gene (*ankA*) were targeted to detect *A. phagocytophilum* [16,17]. All the PCR primers and probes used for detecting bacterial pathogens, PCR conditions, and product sizes are listed in Table 1.

The resulting sequences obtained in this study were examined using the Nucleotide Basic Local Alignment Search Tool (BLASTN) program of National Center for Biotechnology Information (NCBI) (Bethesda, MD, USA) to identify the bacteria present. A phylogenetic tree was constructed using ClustalX (version 2.0) and the Tree Explorer program (DNASTAR, Madison, WI, USA) was run according to the Kimura 2-parameter method utilizing alignments of positive gene sequences and bootstrap analysis (1,000 replicates) to improve the confidence level of the phylogenetic tree. IFA was performed at the Korea Centers for Disease Control and Prevention as described previously [18] to detect IgG and IgM antibodies specific to Q fever, spotted fever, Lyme disease, and anaplasmosis.

Table 1. Oligonucleotide primers and polymerase chain reaction (PCR) conditions.

Species	Target gene[a]	Primer name	Sequence (5′-3′)	Annealing temp (°C)	Size (bp)	Reference
Coxiella burnetii	*IS1111*	IS111F1	TACTGGGTGTTGATATTGC	52	485	[10]
		IS111R1	CCGTTTCATCCGCGGTG			
		IS111F2	GTAAAGTGATCTACACGA	56	260	
		IS111R2	TTAACAGCGCTTGAACGT			
	16S rRNA	16s1s-tF0	AAGAGTTTGATTCTGGCTCAG	56	1,440	This study
		16s1st-R0	AGGTTAGCCTACCCGCTTC			
		Cox16SF1	CGTAGGAATCTACCTTRTAGWGG	56	720	[11]
		Cox16SR1	ACTYYCCAACAGCTAGTTCTCA			
		Cox16SF3	GAGTATGGTAGAGGGAAGTGG	56	790	This study
		Cox16SR2	GCCTACCCGCTTCTGGTACAATT			[11]
Rickettsia species	*ompA*	RR190.70F	ATGGCGAATATTTCTCCAAAAA	50	634	[12,13]
		RR190.701R	GTTCCGTTAATGGCAGCATCT			
		RR190.70F	ATGGCGAATATTTCTCCAAAAA	54	535	
		RR190.602R	AGTGCAGCATTCGCTCCCCCT			
	23S rRNA	PanR8_F	AGCTTGCTTTTGGATCATTTGG	55	110	[14]
		PanR8_R	TTCCTTGCCTTTTCATACATCTAGT			
		PanR8_P	[5-FAM]CCTGCTTCTATTTGTCTTGCAGTAACACGCCA[3-BHQ1]			
Borrelia species	*pyrG*	pyrG-1F	ATTGCAAGTTCTGAGAATA	45	801	[15]
		pyrG-1R	CAAACATTACGAGCAAATTC			
		pyrG-2F	GATATGGAAAATATTTTATTTATTG	49	707	
		pyrG-2R	AAACCAAGACAAATTCCAAG			
Anaplasma phagocytophilum	*groEL*	GRO607F	GAAGATGCWGTWGGWTGTACKGC	54	688	[16]
		GRO1294R	AGMGCTTCWCCTTCWACRTCYTC			
		GRO677F	ATTACTCAGAGTGCTTCTCARTG	57	445	
		GRO1121R	TGCATACCRTCAGTYTTTTCAAC			
	ankA	ANK-F1	GAAGAAATTACAACTCCTGAAG	53	705	[17]
		ANK-R1	CAGCCAGATGCAGTAACGTG			
		ANK-F2	TTGACCGCTGAAGCACTAAC	54	664	
		ANK-R2	ACCATTTGCTTCTTGAGGAG			

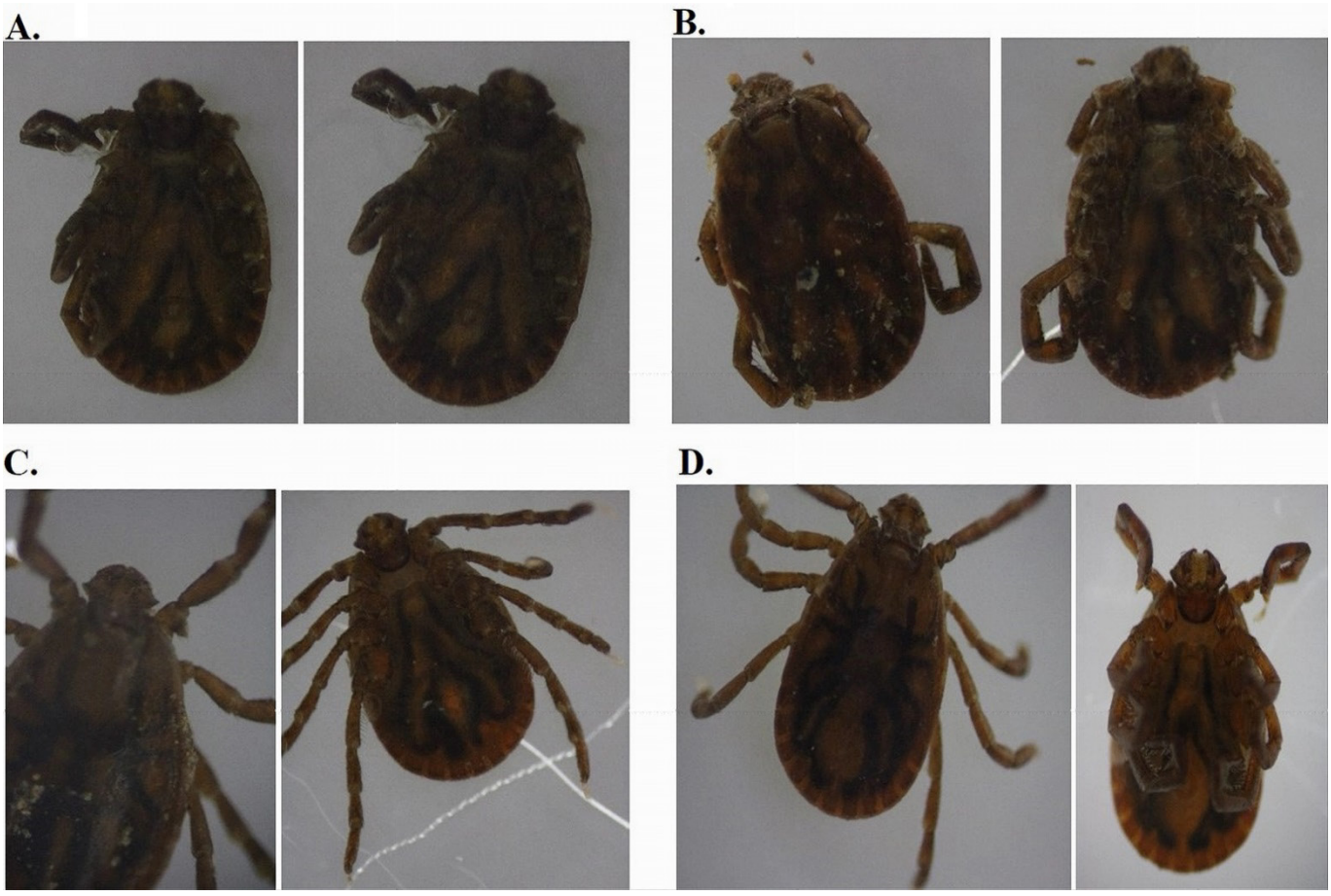
[a]*IS1111: htpAB*-associated repetitive element; *16S rRNA*: 16S ribosomal RNA gene; *ompA:* outer membrane protein A gene; *23S rRNA*: 23S ribosomal RNA gene; *pyrG*: CTP synthase gene; *groEL:* heat shock protein gene; *ankA:* ankyrin-related protein gene.

Table 2. Follow-up indirect immunofluorescence assays (IFA) antibody titer assessment in the 60-year-old patient and polymerase chain reaction (PCR) assays to diagnose Q fever, spotted fever, Lyme disease, and anaplasmosis in patient blood specimen and the four ticks.

		Q fever				Spotted fever				Lyme disease			Anaplasmosis			
Sample	**Sampling day**	***16S rRNA* N-PCR**	***IS1111* N-PCR**	**IFA IgG Phase I/II**	**IFA IgM Phase I/II**	**PanR8 Q-PCR**	***ompA* N-PCR**	**IFA IgG**	**IFA IgM**	***pyrG* N-PCR**	**IFA IgG**	**IFA IgM**	***groEL* N-PCR**	***ankA* N-PCR**	**IFA IgG**	**IFA IgM**
Patient	22-Apr	P	N	(−)/(−)	(−)/(−)	N	N	n/d	n/d	N	n/d	n/d	N	N	n/d	n/d
	23-Apr			n/d	n/d			n/d	n/d		(−)	(−)			(−)	(−)
	27-Apr			(−)/(−)	(−)/1:512			n/d	n/d		(−)	(−)			(−)	(−)
	9-May			(−)/1:1024	(−)/1:1024			n/d	n/d		(−)	(−)			(−)	(−)
	7-Jun			(−)/>1:2048	(−)/>1:2048			n/d	n/d		(−)	(−)			(−)	(−)
				Development stage				Microscopic identification			Molecular identification					
Tick1	5-May	P	N	Adult female		36	P	*H. longicornis*			*H. longicornis*		N	N		
Tick2	5-May	N	N	Adult female		n/d	P	*H. longicornis*			*H. longicornis*		N	N		
Tick3	5-May	P	N	Adult female		n/d	P	*H. longicornis*			*H. longicornis*		P	N		
Tick4	5-May	P	N	Adult female		n/d	N	*H. longicornis*			*H. longicornis*		N	N		

(−): < 1:16; n/d: not determined; P: PCR positive; N: PCR negative; N-PCR: nested-polymerase chain reaction.

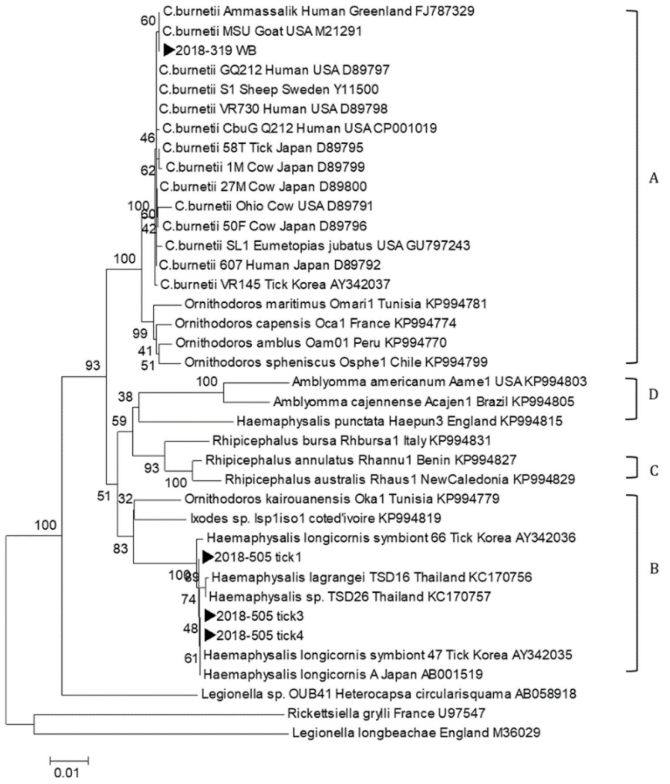
Figure 1. Micrographs of four ticks collected in this study. The images were acquired using a Stemi 508 stereomicroscope (Carl Zeiss Microscopy GmbH, Jena, Germany) at 25.6× magnification. The four ticks were found in the workplace of the patient after his hospitalization. A represents 2018-505-tick1. B represents 2018-505-tick2. C represents 2018-505-tick3. D represents 2018-505-tick4. According to morphological classification and molecular identification, the ticks were identified as adult female *Haemaphysalis longicornis*.



Discussion

C. burnetii infection in human is usually asymptomatic or presents as a mild illness with flu-like symptoms. Although the patient was asymptomatic, IFA results indicated that the patient had Q fever. Since 60% of patients with acute Q fever are asymptomatic, serological evidence is more important than clinical manifestations for diagnosis [19]. The four collected ticks were all identified as adult female *Haemaphysalis longicornis* (Figure 1) using morphological and molecular biological methods targeting the *16S rRNA* [20]. N-PCR and real-time PCR analyses were all negative for vector-borne infectious diseases except for *Coxiella* species-specific *16S rRNA* N-PCR (Table 2). The sequencing results confirmed the presence of *C. burnetii*. Homology assessment showed that the *16S rRNA* sequence of the sample from the *Coxiella*-positive patient exhibited 99.9% similarity to the *16S rRNA* partial sequence of *C. burnetii* strain MSU isolated from a goat in the United States. The results of the follow-up investigation of the IFA data revealed that the patient had developed antibodies against *C. burnetii*, but had no antibodies against spotted fever, Lyme disease, or anaplasmosis. The patient showed ≥ 4-fold increase in both IgM and IgG antibody titers against *C. burnetii*.

Figure 2. Phylogenetic tree based on partial *16S rRNA* sequences (1210 bp) from GenBank and Coxiella-positive patient and three ticks collected in this study (▶). 2018-319 WB represents the bacteria infecting the patient, which was found to *be Coxiella burnetii*. Further below, the bacteria isolated from the ticks, 2018-505-tick 1, 3, and 4, are indicated. All ticks collected in this study were *Haemaphysalis longicornis* and they carried Coxiella-like bacteria (CLB), instead of *C. burnetii*. Coxiella clades (A–D) are indicated at right. Scale bars indicate 0.01 base substitutions per site. GenBank accession numbers are shown in the tree.



The *Coxiella* species-specific *16S rRNA* N-PCR was positive for three ticks (2018-505-tick1, -tick3, and -tick4), and sequencing results confirmed the presence of a *Coxiella* endosymbiont. The *Coxiella* sp. harbored in the three ticks were identified as *Coxiella*-like bacteria (CLB) and not *C. burnetii*. Homology testing showed that the *16S rRNA* sequences of the three *Coxiella*-positive ticks (2018-505-tick1, -tick3, and -tick4) had 99.8%, 100%, and 100% similarity, respectively, to the *16S rRNA* partial sequence of *H. longicornis* symbiont 47.

In Korea, *H. longicornis* was the first tick to harbor *Coxiella* spp. [21]. However, CLB and *C. burnetii* share strong genetic similarity, despite their distinct ecological features [11]. Even if *Coxiella* spp. are found in ticks, and genetic and serological tests are performed, it is difficult to determine whether they are *C. burnetii* or CLB before checking the phylogenetic tree. Therefore, a phylogenetic tree was constructed using sequences of *16S rRNA* gene fragments (1210 bp) from the patient's blood sample and three *Coxiella*-positive tick samples, with the *16S rRNA* gene sequences of *C. burnetii* and CLB from GenBank as reference sequences. Finding the same bacterium in any of the four ticks would indicate a chance of transmission of *C. burnetii* infection to the patient by a tick. After analyzing the phylogenetic data, we concluded that the infection was not tick-borne. The *16S rRNA* gene sequences from the *Coxiella*-positive patient samples clustered with *C. burnetii* sequences. All *16S rRNA* gene sequences from *Coxiella*-positive tick samples clustered with CLB from *H. longicornis* ticks (Figure 2).

To our knowledge, there are no reports of tick-borne *C. burnetii* infections in Korea. In conformity with this background, the patient in our study does not appear to have been infected by tick borne *C. burnetii*. We also note that two of the ticks studied carried more than one bacterium in addition to CLB. 2018-505-tick 1 carried both *Rickettsia* and *Coxiella*, and 2018-505-tick 3 carried *Rickettsia*, *Anaplasma*, and *Coxiella*. Concomitant infection with *C. burnetii* and other *Rickettsia* species is also possible [22]. If a patient is infected with *C. burnetii* by ticks, infection with other

Rickettsia and *Anaplasma* bacteria is highly likely. In this case study, the results are negative. Consequently, our patient was serologically positive for Q fever. This fact supports the idea that he was not infected with *C. burnetii* through ticks but from other sources. In some cases, a tick may have a pathogen but lack the ability to transmit it. As *C. burnetii* and CLB have genetical similarity, we have to find out the reason of infection in more cases from South Korea, that can be possible either by sequential transmission or through contaminated aerosols or consumption of raw milk from infected animals. Tick-borne transmission thus requires further study.

One limitation is that we cannot rule out the possibility that the ticks found on the patient's body may have carried *C. burnetii*. We also cannot rule out the possibility of missing ticks carrying *C. burnetii*. Only ticks harboring CLB, but not *C. burnetii*, were found on the patient's lawn. In addition, since many patients with acute Q fever in South Korea have been confirmed to have no history of contact with animals or occupational risk [23], the possibility of infection through the inhalation of *C. burnetii* or the ingestion of raw milk from infected animals cannot be ruled out. Further investigation is required to identify the carriers or transmitters of this infection.

Conclusions

Here, we describe a case in which a patient was infected with *C. burnetii* and manifested symptoms of Q fever. A *Coxiella*-specific *16S rRNA* N-PCR was performed, and four ticks were collected from the suspected location where the tick bite occurred. Our study suggests that the *C. burnetii* strain isolated from the patient differs from the CLB isolated from *H. longicornis*. We thus concluded that the patient with Q fever was not infected with *C. burnetii* via tick bites.

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Authors' contributions

Concepts: CMK, DMK; Design: DMK; definition of intellectual content: DMK; literature search: CWK, CMK, and SC; clinical studies: CWK, NRY, and DMK; experimental studies: CWK and CMK; data acquisition: CMK, NRY, DMK, and SC; data analysis: CMK and DMK; statistical analysis: CWK, CMK, NRY; manuscript preparation: CWK, CMK, NRY, DMK, SC; manuscript editing: CMK, NRY, and DMK; manuscript review: CMK, DMK, and NRY

Ethics approval

This study was approved by the Ethics in Human Research Committee of Chosun University Hospital (IRB No. 2013-10-001-018).

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