

Acute Q Fever With Dermatologic Manifestations, Molecular Diagnosis, and No Seroconversion

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We herein described a case of acute infection by *Coxiella burnetii* (acute Q fever) that started with a short incubation period and showed prominent dermatological manifestations and unusual serological behavior. The infection was confirmed by molecular detection through real-time polymerase chain reaction using genomic DNA collected from peripheral blood.

Keywords. acute Q fever; *Coxiella burnetii*; dermatologic manifestations; molecular diagnosis; seroconversion.

CASE PRESENTATION

The patient was a 50-year-old zootechnician who had exclusively worked as a university professor for the last 3 years with no other relevant history. His recent travel history included a 4-day trip to a tropical rural area in Magdalena Medio in the department of Antioquia (Colombia), where he was in direct contact with different animals, particularly a goat that had recently given birth. Further, he had participated in recreational aquatic activities such as swimming in a pool and a river. He reported not being bitten by a tick or consuming unpasteurized dairy products.

Later, 72 hours after being in contact with the goat, he had persistent fever of 38.2°C, chills, diaphoresis, and myalgia. On day 2 of disease, he attended a consultation wherein severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was ruled out (negative antigen and reverse transcription polymerase chain reaction [RT-PCR] test results). On day 3 of disease, a reddish maculopapular, nonpruritic rash appeared on his upper limbs. A week after the onset of symptoms, he reported persistent fever that reached 41.4°C and 2–3 liquid bloodless bowel movements every day along with dry cough; thus, he was hospitalized. The following possible clinical etiologies were ruled out: dengue infection (negative NS1 and immunoglobulin M [IgM] enzyme-linked immunosorbent assay [ELISA]), malaria (negative thick blood smear), and typhoid fever (2 negative blood cultures for aerobic organisms and negative stool test). On day 8, the rash was generalized, mostly purpuric, and coalesced in the distal third of the lower limbs (Figures 1 and 2). Physical examination showed enanthem on the soft palate, scarce crepitus in the upper third of the right hemithorax, and painless hepatomegaly with no further positive findings.

Laboratory Tests

The laboratory test results were as follows: white blood cells, 4270 (normal: 4000–11 000/μL); neutrophils, 3180 (normal: 1500–7700/μL); lymphocytes, 710 (normal: 1000–4000/μL); hemoglobin, 13.1 (13.6–16 g/dL); platelets, 186 000 (normal: 150 000–450 000/μL); C-reactive protein 22 (normal: <3 mg/dL); creatinine, 1.11 (normal: 0.9–1.1 mg/dL); aspartate aminotransferase (AST), 165.9 (normal: <33 U/L); alanine aminotransferase (ALT), 136 (normal: <36 U/L); gamma-glutamyl transferase, 243 (normal: <40 U/L); direct and total bilirubin and alkaline phosphatase levels were normal. Acute infection by *Rickettsia* spp. or *Coxiella burnetii* was suspected, and a whole-blood sample was collected on day 7 of symptoms for DNA extraction using the Dneasy Blood and Tissue QIAGEN kit. Two real-time PCR tests were conducted (using protocols and reagents for in vitro research) to amplify the *gltA* gene for *Rickettsia*, which encodes citrate synthase [1], and the IS1111 insertion sequence for *C. burnetii* [2]. This last PCR protocol has been previously used to diagnose *C. burnetii* in Colombia and uses a probe containing a minor groove binding (MGB) molecule, forming an extremely stable duplex and giving the probe a significant increase in melting temperature [3]. The commercially available DNA controls AMPLIRUN *Rickettsia conorii* and AMPLIRUN *Coxiella burnetii* were used as positive controls, and Type 1 Milli-Q water (Merck, Darmstadt, Germany) was used as a negative control. These protocols were

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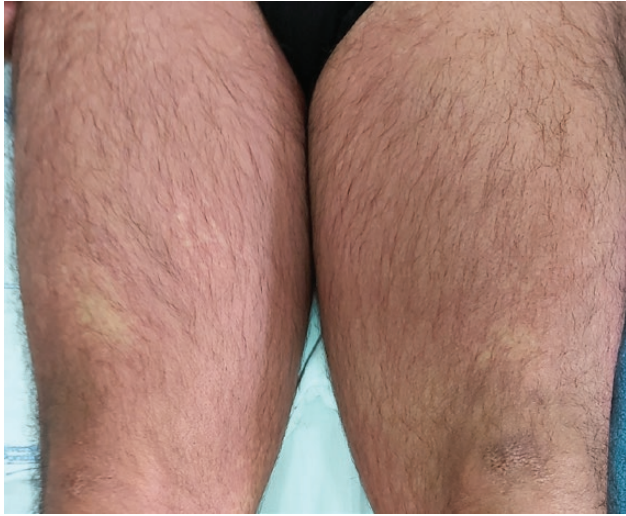


Figure 1. Reddish maculopapular, nonpruritic rash on both thighs.

performed using CFX96 Touch Real-Time PCR Detection System equipment (BIORAD, USA). The blood sample taken from the patient was negative for *Rickettsia* and positive for *C. burnetii* (Figure 3). On day 11 of evolution, chest computerized axial tomography was performed, which confirmed multilobar pneumonia primarily located in the upper right lobe (Figure 4).

On day 13, the patient experienced dyspnea on minimal exertion and desaturation requiring low supplemental oxygen therapy. When the PCR for *C. burnetii* returned with a positive result, the patient was started on doxycycline 100 mg twice a day.

Fever decreased within 2 days of treatment, purpuric rash on the lower limbs disappeared on day 4, dyspnea disappeared on day 5, and the remaining skin lesions completely disappeared within 6 days of treatment. On day 17 of symptoms, immunofluorescence assay IgG antiphase I and II *C. burnetii* antibodies (Focus Diagnostics, Inc, Cypress, CA, USA; titer <1:16, negative result <1:16) and IgG anticardiolipin antibodies (4 GPL/mL, negative <17 GPL/mL) were both negative. Echocardiography revealed no valve lesions, and transaminase levels improved. Supplemental oxygen therapy was discontinued, and the patient was discharged after day 7 of treatment with no symptoms to complete 14 days of doxycycline. Rash, hepatomegaly, and lung infiltrates had resolved at the time of the follow-up 1 month after discharge. Four weeks later, a new test for convalescent antiphase I and II *C. burnetii* IFA IgG was negative.

DISCUSSION

We herein described the case of a patient with acute Q fever with a short incubation period, prominent dermatological manifestations, and unusual serological behavior. This infection was caused by *C. burnetii* zoonotic bacteria, which are

gram-negative bacteria, although they are not colored by the usual dye [4]. *C. burnetii* zoonotic bacteria are obligate intracellular bacteria, and their most significant reservoirs are sheep, goats and cows. This bacteria can be transmitted with humans, are sheep, goats, and cows because these bacteria can be transmitted via aerosols generated after infected animals give birth or undergo abortions as well as by direct contact with fluids such as feces, urine, and milk [5, 6]. The form adopted by these bacteria, similar to a spore, can spread up to 18 km from the source of infection [7]. In addition, *C. burnetii* zoonotic bacteria can be transmitted by consuming unpasteurized dairy products or contaminated meat. They can survive in powdered milk at room temperature for up to 40 months and up to 1 month in meat under refrigeration [8]. *C. burnetii* zoonotic bacteria are present worldwide, except for New Zealand [9]. Given their low infectious dose for humans (as low as 1.8 bacterial cells), many hosts, and different transmission mechanisms, the Centers for Disease Control and Prevention classified these bacteria as a category B bioterrorism agent [10]. To date, the most significant outbreak reported worldwide occurred between 2007 and



Figure 2. Purpuric rash in the distal third of the lower limbs (picture taken on day 8 of symptoms).

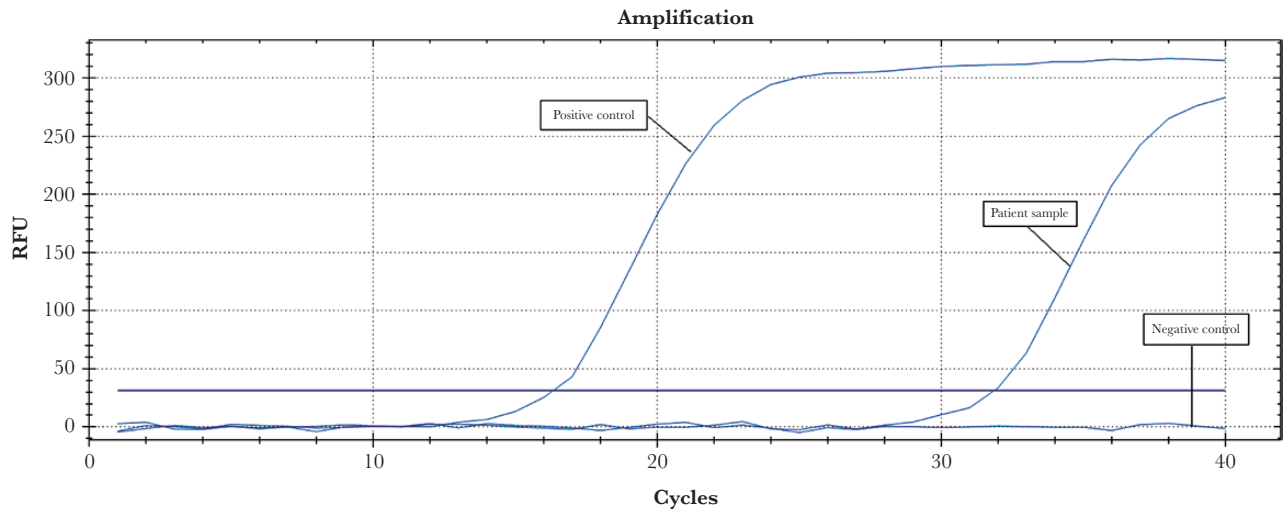


Figure 3. Real-time PCR result for *C. burnetii* detection. Red line: commercially available positive DNA control; black line: Milli-Q type I water negative control; green line: patient's positive result with a cycle threshold of 31.8. Abbreviations: PCR, polymerase chain reaction; RFU, Relative Fluorescence Units.

2010 in the Netherlands, when up to 4000 cases were reported in humans [11].

The incubation period for this infection varies, reaching a median of 18 days; 95% of acute infection cases appear between days 7 and 32, with extreme periods of 2–60 days [12]. Moreover, 60% of cases have been documented to be asymptomatic, 40% of patients will develop mild symptoms, and 5% will show severe symptoms [13]. Acute Q fever most commonly presents as fever, similar to a flu with sudden onset of symptoms, lasting up to 15 days. It can also cause pneumonia with significant extrapulmonary signs and symptoms and hepatitis that is not usually accompanied by jaundice; however, if present, it is associated with delayed defervescence following treatment initiation [14].

In Colombia, few cases have been reported, most of them of the chronic form, particularly in association with endocarditis

[15, 16]. The acute form is practically unknown among doctors in the Colombia, and just 1 case of acute infection has been reported to the best of our knowledge [17]. As of 2006, a seroprevalence of 23.6% was reported in rural workers from the north of the country [18]. Recently, molecular detection by real-time PCR based on amplification of the IS1111 insertion sequence of *C. burnetii* was performed, following the same protocol as used in the present case. This test analyzed peripheral blood collected from asymptomatic farmers and their cattle and yielded 25.9% and 19.5% positivity, respectively [3].

The frequency of each clinical manifestation is associated with its way of transmission and geographical location [13]. Rickettsial diseases, which are typically associated with fever, rashes, and vasculitis [19], have been differentiated from Q fever, as the former affect the skin in 84%–91% of cases [20], whereas in the latter skin alterations are typically not observed. However, skin manifestations have been reported in adults with Q fever in 5%–21% of patients in case series described in France and 9% in Israel [21]. Accordingly, if skin manifestations occur, they mainly produce maculopapular rash, purpuric or vesicular, or less common forms such as erythema nodosum [22], granulomatous lobular panniculitis [23, 24], erythema-annulare-centrifugum [25], or leukocytoclastic vasculitis. Our patient showed both maculopapular and purpuric lesions; although the associated pathophysiological mechanism has not been clearly described, this phenomenon may have been triggered by vasculitis, as with *Rickettsia* spp. infections.

There are different methods for confirming the diagnosis, most of which are not widely available or are expensive. According to the US Centers for Disease Control and Prevention laboratory criteria, acute Q fever is confirmed by a positive result in any of the following cases: (a) 4-fold change in the titer of antiphase II *C. burnetii* IgG antibodies observed by immunofluorescence

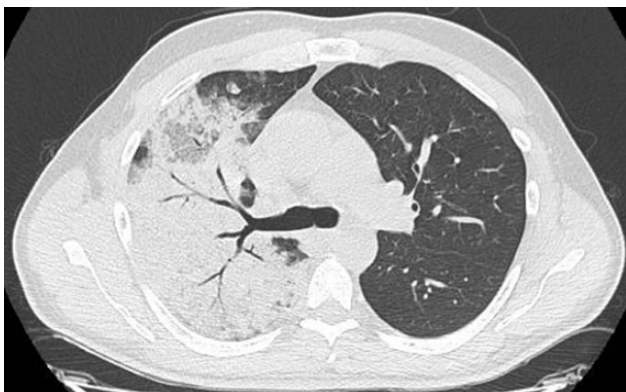


Figure 4. Chest computerized axial tomography showing multilobar consolidation, primarily in the right upper lobe.

between paired sera; (b) *C. burnetii* DNA detected in a clinical sample by PCR; (c) *C. burnetii* evidenced in a clinical sample by immunohistochemistry; and (d) *C. burnetii* isolation from a clinical sample by cell culture [14].

This infection is currently detected mostly (although not exclusively) by serological and molecular tests. Indirect immunofluorescence assays are mainly used because they have 98.9% sensitivity and 97.7%–100% specificity [26], although it should be considered that up to 5% of patients do not develop antibodies [26], particularly those who are treated early. Antiphase II IgM is expected to be detectable at days 5–7 of the disease. Generally, on day 21, 90% of patients are positive for 1 of the 2 types of antibodies; however, false positives may occur in cytomegalovirus and Epstein-Barr virus infections [27]. Finally, the avidity test may be helpful to differentiate an acute infection from its convalescent phase [8].

For PCR, 81% sensitivity, 90% specificity, and 87% positive predictive value have been reported [28]. For this test, only 10–100 bacteria are required per sample, and one of the most used genes in literature is the IS1111 insertion sequence because each bacterium has 7–110 copies in its genome, which increases the sensitivity of the test. It should be noted that positive results have been obtained up to day 17 of disease because antibodies have a neutralizing effect on *C. burnetii* that hinders its detection [8, 13]; polymerase inactivation has been reported when the number of antibodies is >25 600 [8]. Moreover, negative results are obtained 24–48 hours after treatment initiation [14]. In our case, the high PCR positivity found in some populations in Colombia could suggest that the PCR-positive DNA was not related to incident disease but represented the unusual background of PCR positivity in the population. However, this possibility is highly unlikely because the patient did not live in a high-prevalence area, had a rapid response to treatment, and a risk exposure was identified.

As confirming the diagnosis and interpreting serological tests are complex, the most relevant approach at present is a combination of molecular and serological methods, although they have demonstrated a poor correlation [14, 24]. This case is an example of the inconsistency between the negative results obtained for paired serology of antiphase II IgG antibodies and PCR positivity, which could be explained by the fact that the patient received early diagnosis and management. Unfortunately, antiphase II IgM antibodies could not be measured.

The most efficient treatment for Q fever is doxycycline [29]. Fluoroquinolones, trimethoprim-sulfamethoxazole, and clarithromycin have also proven effective; however, azithromycin is not recommended due to its high minimum inhibitory concentration (8 mg/L). Successful use of tigecycline and linezolid has also been reported [24].

Doxycycline should be prescribed at 100 mg twice a day for 14 days [14], and experts recommend [24] transthoracic echocardiography in all patients to determine the individual risk of

developing endocarditis during the acute phase of the disease. In patients aged >40 years with >75 IU anticardiolipin, IgG antibodies or >3200 antiphase II IgM antibodies, and normal transthoracic echocardiography, a transesophageal echocardiogram is recommended, and if any echocardiographic abnormality is detected, doxycycline prophylaxis is recommended for 1 year. In patients with known valve disease, prosthetic valves or high-risk echocardiographic abnormalities observed on transthoracic echocardiogram (bicuspid aortic valve, mitral valve prolapse, valve failure or stenosis grade ≥ 2 , or valve remodeling or thickening), prophylaxis with doxycycline is recommended, and no transesophageal echocardiography is needed [24]. Based on assessment, it was determined that our patient did not present any risk factors for endocarditis within the acute Q fever context; thus, just serological follow-up for 6 months was planned.

Notes

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Patient consent. The patient signed an informed consent to authorize the publication of his case and related pictures. No formal approval by an ethics committee is required for this type of paper (“ID Teaching Cases”).

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