

Serologic detection of a rare case of Q fever in New York City having hepatic and unusual renal complications

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Abstract We describe the case of a 46-year-old resident of New York City with a one-year history of frequent urination and 3 weeks of undulating fevers. He also had liver and bone marrow abnormalities where a non-culturable Gram-negative rod was identified. Q fever was suspected and confirmed based on highly elevated phase I and II serum IgM/IgG antibodies against *Coxiella burnetii*.

Keywords Q fever · *Coxiella burnetii* · Zoonotic disease

Introduction

Q fever is most often contracted after humans inhale infected dust particles, handle infected animal tissues, such as urine, feces or birth products, or ingest milk contaminated with *C. burnetii* [11]. Originally considered to be a member of the *Rickettsia* family, *C. burnetii* appears now to be more closely related, based on limited genetic studies

[11], to *Legionella* and *Francisella*, as part of the gamma subdivision of proteobacteria. Phenotypically, however, it has strong rickettsia-like properties based on its intracellular life cycle and its inability to grow in vitro on artificial media into disease causing forms. *C. burnetii* is widely distributed in nature as a zoonoses in ticks, small wild animals, and certain farm animals such as cattle, goats and sheep.

Q fever occurs worldwide but most cases are reported from Australia, England and various Mediterranean countries, especially France. It is, however, uncommon or infrequently reported throughout most of North America, including the United States [13], although intermittent outbreaks have occurred [10] in certain parts of Canada, especially within the eastern Maritime provinces for about the last 15–20 years. The reported prevalences, however, are highly dependant upon local interest of the medical community to this specific disease (especially the presence of a reference center for Q fever).

The usual target area of disease in Q fever is the lungs, although only about one-half of all people infected with *C. burnetii* show signs of clinical illness [11]. Disease onset is usually abrupt with a high and prolonged fever, severe headache, and various influenza-like symptoms such as myalgia, sore throat, chills, sweats, and a non-productive cough. Other usual acute clinical presentations include atypical pneumonia and acute hepatitis. Pneumonia ensues following entry of the pathogen into the lungs and subsequent infection of the alveolar macrophages. Chronic disseminated infections can occur leading to hepatitis and endocarditis, with organisms persisting in cardiac valves which could lead to a life-threatening illness [9]. Many other organs may be involved and other possible, but rare, complications include glomerulonephritis, osteomyelitis, and neurologic abnormalities [2, 3, 16].

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Case presentation

In April 2006, a 46-year-old Guyanese man, who was residing in the Queens section of New York City (NYC), was admitted to our hospital because of persisting fever of 2 weeks duration and a 1-year history of frequent urination having little or no pain or discomfort. The patient was referred to us after being under the care of another health care provider for the previous 2 weeks. There, he had also received empiric treatment with oral ciprofloxacin (250 mg, twice daily) for 1 week, for a suspected urinary tract infection, without any clinical improvement of his urinary symptoms. There was also no significant deferescence and, for the past 2–3 weeks, he had undulating fevers (ranging from 101 to 104°F; Fig. 1), chills and drenching sweats. He did not have a headache, cough, diarrhea, abdominal or flank pain, or other focal signs of infectious origin. He did not have a history of nephropathy, abnormal serological findings, rashes, edema, insect bites or known contact with farm animals or household pets. He did not consume any unpasteurized dairy products or alcohol or use tobacco, and had not traveled outside the United States for the past 20 years. On physical examination the patient appeared in moderate distress, but was anicteric. His blood pressure was 95/60 mmHg, and auscultation of the lungs and heart did not reveal any chest abnormalities. His neck was supple with no cervical adenopathy, and the abdomen was soft and non-tender with positive bowel sounds and no organomegaly.

Laboratory studies on admission revealed the following: erythrocyte sedimentation rate, 84 mm/hr; leukocyte count, 14,200/mm³ (71% neutrophils, 24% lymphocytes, 4% monocytes, and 1% eosinophils); platelet count, 52,400/mm³;

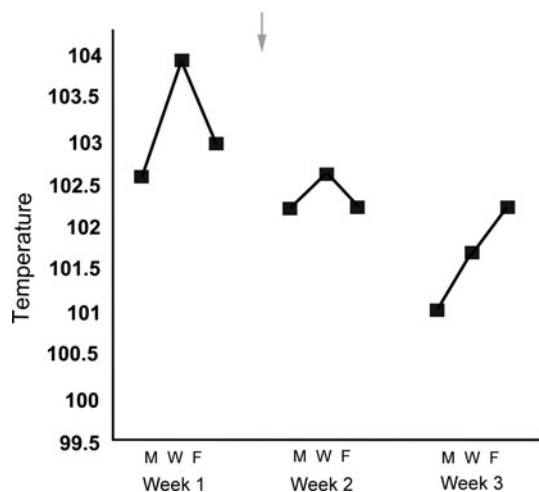


Fig. 1 Patient's fever chart during his initial 3-week observation period. The arrow indicates the beginning of treatment with ciprofloxacin (of one week duration) and the temperature values are in degrees Fahrenheit. M Monday, W Wednesday, F Friday

hemoglobin, 12.6 g/dL; hematocrit, 36.3%; albumin, 3.0 g/dL; aspartate aminotransferase, 64 U/L; alanine aminotransferase, 137 U/L; alkaline phosphatase, 114 U/L; lactate dehydrogenase, 500 U/L; total bilirubin, 1.55 mg/dL; and direct bilirubin, 1.04 mg/dL. Urinalysis revealed slight hematuria (30–40 RBCs per high power field); 2–5 leukocytes per high power field; and mild proteinuria (0.3 g/dL). There was no growth of bacterial pathogens on routine blood and urine cultures using thioglycollate broth, blood agar, MacConkey agar, and chocolate agar. These were incubated for up to 10 days. Analysis of Giemsa-stained peripheral blood smears revealed no intracellular bacteria or parasites such as *Ehrlichia* or *Anaplasma*.

The patient was not given a PPD skin test since he recalled being vaccinated with BCG when he was a child. An RPR test for syphilis was non-reactive.

No pleural effusions or infiltrates were observed on chest roentgenograms or a CT scan, although a CT scan of the head revealed chronic sinusitis. An abdominal CT scan revealed hepatosplenomegaly, fatty infiltration of the liver, scattered diverticula, but no diverticulitis, and no adenopathy. Biopsy studies done on the liver showed non-necrotizing fibrin-ring granulomas, moderate fatty metamorphosis, no lymphoma or other malignant cells, and no acid-fast staining bacilli or fungi. Biopsy studies done on the bone marrow revealed hypercellularity with granulomatous changes, and the presence of intracellular coccobacilli and extracellular Gram-negative coccobacilli, based on using the Gimenez modification [5] of the Gram stain procedure. Most Gram-negative bacteria can be seen on the routine Gram stain. The Gimenez technique can show the presence of bacteria, especially those in eukaryotic cells, but it cannot differentiate Gram-negative from Gram-positive bacteria.

Cultures of biopsied bone marrow using thioglycollate broth, blood agar, MacConkey agar, and chocolate agar were negative. Some of these cultures were maintained for up to 10 days to allow for possible growth of slow-growing pathogens such as *Brucella* bacteria.

Serologic testing for Q fever demonstrated both elevated IgM and IgG titers for *C. burnetii* phase I and phase II

Table 1 Serologic test results for possible *C. burnetii* and rickettsial infections based on immunofluorescence assay

Antigen	Antibody titer ^a	
	IgM	IgG
<i>C. burnetii</i> phase I	256	128
<i>C. burnetii</i> phase II	1,024	1,024
<i>Rickettsia rickettsia</i> (RMSF)	<32	64
<i>Rickettsia typhi</i> (typhus)	<32	<32

^a Data are reported as the reciprocal of the highest dilution having a positive reaction

antigens (Table 1), based on results from a commercially available rickettsial panel immunofluorescence assay (Focus Diagnostics, Cypress, CA, USA). There was also borderline reactivity for IgG antibodies directed against the agent for Rocky Mountain spotted fever (RMSF), but no reactivity against typhus. The validity of these test results was based on using known positive and negative control samples that were provided in the manufacturer's test kit. A diagnosis of Q fever was made and the patient was treated successfully with doxycycline (100 mg b.i.d. orally for 2 weeks). He quickly deconvalesced, 2 days later, then became afebrile 4 days after treatment began, and his urination patterns returned to normal. He appeared in good health at his follow-up visit, one month later. Due to his rapid response to therapy, no further analyses of possible renal complications associated with glomerulonephritis were done.

Discussion

In this case report, we describe a patient having an unusual presentation of Q fever where there were subtle renal abnormalities, consistent with borderline glomerulonephritis, along with granulomatous hepatitis, based on abnormal liver function tests and histopathological analysis of a biopsied tissue specimen. Also because of the unusual clinical presentation of our patient, it is possible that some of the urinary-related symptoms were due to a low-grade, generalized form of vasculitis or autoimmune type of phenomena, either unrelated to *C. burnetii* infection or triggered by some as yet to be identified pathogen-induced host response. It is noteworthy that such renal abnormalities have been rarely reported in the absence of the chronic complications of Q fever endocarditis, but can be associated with the presence of antibodies to phospholipids [18]. With regards to Q fever hepatitis, it has been shown [20] that there is no progression to cirrhosis, but some degree of fatty changes occur, and fibrin-ring granulomas can persist for up to 3 years. Also persisting are abnormal liver function test results, despite the patient being asymptomatic. No signs of hepatic cell necrosis have been observed in either acute or chronic Q fever hepatitis. A recent report [8], however, suggests that *C. burnetii* could trigger autoimmune liver disease and be involved with the pathogenesis of subsequent liver damage.

Apart from radiologic evidence for chronic sinusitis, our patient had no serious respiratory involvement typically associated with Q fever such as pneumonia. Other significant physiologic test results included leukocytosis, thrombocytopenia and moderate hyperbilirubinemia. Serologic findings were diagnostic for acute Q fever, based on well established published criteria [17], with significantly high

titers of phase II antibodies and positive phase I and II IgM antibodies, which were consistent with the identification of a non-culturable, Gram-negative short rod in the bone marrow. Our patient's condition resolved rapidly after receiving appropriate short-term antimicrobial therapy: a result more indicative of acute rather than chronic Q fever. Brucellosis was also strongly considered in the early differential diagnosis of our patient, based initially on the undulating fever pattern and sweats, ineffectiveness of ciprofloxacin, and then subsequently, by the abnormal liver findings and the presence of Gram-negative bacilli in the bone marrow. This zoonotic infection, however, is also extremely uncommon in the NYC area [1], and the negative culture results and rapid response to short course therapy with doxycycline excluded it as a possible cause of our patient's non-specific febrile illness. Our patient's chief complaint suggested chronic renal dysfunction with the development of mild hematuria and proteinuria which are typically associated with an ascending urinary tract infection. Such findings are infrequent but have been reported to be associated with chronic Q fever endocarditis [6, 9, 19] and rarely due to an acute *C. burnetii* infection as part of the pathogenesis of glomerular disease [18]. Accordingly, since cardiopulmonary findings were unremarkable in our case, chronic Q fever endocarditis was an unlikely contributing factor, or as the focal source of persisting organisms. Rather, it would seem that the re-emergence of *C. burnetii* organisms from our patient's bone marrow, following a prior asymptomatic infection, led to symptomatic illness. To our knowledge, only two other previously published cases reported similar findings [9, 20], with the isolation of *C. burnetii* from bone marrow in what may have been a chronic-like form of Q fever granulomatous hepatitis. On the other hand, because of the stability of *C. burnetii* in the environment, our case could have been attributed to a recent, newly contracted infection rather than the recrudescence of a much earlier exposure.

Our patient's poor response to ciprofloxacin seems inconsistent with its reported efficacy, based on a few case studies, against acute forms of Q fever [11]. There is, however, a recent report [15] that describes treatment failures of Q fever for certain antibiotics, including ciprofloxacin. In one of these cases, a diabetic patient died from the infection despite receiving ciprofloxacin and other antibiotics.

A particularly intriguing aspect of this case is the manner in which our patient may have acquired his infection since he had no apparent risk factors. He had been a resident of NYC since leaving his native country, Guyana, 20 years earlier. Q fever is not endemic and rarely reported in the NYC area, as well as in other highly urbanized parts of the United States [13]. Only ten human Q fever cases, prior to this one, had been reported in NYC since 1999 [1], when this disease became notifiable

throughout most of the United States [13]. Despite there being no detailed published accounts of these earlier cases, they, along with ours, appeared to be isolated and did not show any suspicious clustering in time or location, thereby making it highly unlikely that bioterrorism played a role. Nonetheless, in compliance with current bioterrorism surveillance requirements, local public health and law enforcement authorities were notified of our patient's diagnosis.

Is it possible that our case involved re-activation of an earlier undiagnosed or asymptomatic infection with *C. burnetii*? Considerable speculation and some published evidence exist on such a possibility [7, 9]. Our patient denied any contact with potentially infected ruminant animals (the major reservoir hosts for *C. burnetii*), dogs or cats, or traveling to or visiting enzootic parts of the United States or elsewhere. Recreationally, he was a frequent visitor of local city parks. Perhaps for unexplained reasons, our patient did not want to disclose any recent travel to an area where he could have been exposed to *C. burnetii*. He also did not provide any relevant information on where he had lived originally in Guyana or his past medical history there, other than remembering receiving his routine childhood vaccinations including BCG, and having the typical illnesses (mostly flu-like) associated with early childhood and adolescence. Limited information exists on the epidemiology of Q fever in Guyana and some of its neighboring countries of South America [4, 14]. The disease is infrequently reported there, although a seroepidemiologic study [4] conducted from 1992 to 1996 showed an increased incidence with rates higher in the capital city of Cayenne than in rural areas. It was speculated that airborne contamination from rural areas was possible due to the location of Cayenne near the Atlantic Ocean and the contribution of the prevailing off-shore winds. In this regard, reactivation of a previous *C. burnetii* infection has been only documented in pregnant women and seems likely in patients with Q fever endocarditis as a primary clinical manifestation [11]. While possible, acute Q fever due to reactivation of a previous infection seems less likely to occur.

Similar to *Chlamydia* and rickettsial bacteria, *C. burnetii* is an obligate intracellular pathogen [11], but its extracellular form is extremely stable, being able to survive in nature for extended periods where it is able to resist harsh environmental conditions. It is a small pleomorphic coccobacillus that stains weakly using the Gimenez-modified Gram stain procedure [5], which is consistent with the type of organism identified in our patient's bone marrow. Ultrastructural studies reveal a thin Gram-negative cell wall, and at least three forms have been identified: a small cell variant, a large cell variant, and an atypical spore-like form [12]. Its inability to grow on conventional culture media such as blood, MacConkey and chocolate agars

correlated well with a fastidious obligate intracellular organism. Our case emphasizes the need to consider such a pathogen as the possible cause of unusual fever patterns, chills and urinary and hepatic abnormalities, especially in the absence of any clear-cut supporting epidemiologic evidence, along with reinforcing the usefulness of serologic testing in confirming the diagnosis of an atypical presentation of Q fever.

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Conflict of interest statement None.

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