Atypical Manifestations of Chronic Q Fever

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Chronic Q fever is uncommon, with the majority of cases manifesting as culture-negative endocarditis. In this report, we describe 3 patients who present with atypical manifestations of chronic Q fever. These were a 43-year-old man whose site of chronic Q fever was the central nervous system, a 53-year-old woman who underwent coronary angioplasty 6 days before the onset of symptoms of acute Q fever and within 4 months had serologic evidence consistent with chronic Q fever, and a 66-year-old man with fever of unknown origin, a pancreatic mass, and aorto-bifemoral grafts.

Q fever is a worldwide zoonosis caused by the obligate intracellular pathogen *Coxiella burnetii* [1]. *Coxiella* has been isolated from many wild and domestic animals; however, human infection usually is the result of exposure to infected cows, goats, sheep, and cats [2–17]. Although *C. burnetii* infection in animals may cause abortions and stillbirths, most animals have a relatively asymptomatic, persistent subclinical infection [11]. In humans, acute *C. burnetii* infection may be asymptomatic or manifest as a self-limiting febrile illness, pneumonia, or hepatitis [18]. Although the majority of these cases will resolve without sequelae, endocarditis, granulomatous hepatitis, osteomyelitis, and endovascular infections are all uncommon but well-documented chronic manifestations of *C. burnetii* infection [19–23]. We report 3 patients with unusual manifestations of Q fever.

**PATIENTS AND METHODS**

**Patient 1.** This 43-year-old male construction worker presented on April 14, 1999, with a 5-day history of a mild headache and a 4-day history of fevers, chills, fatigue, anorexia, malaise, and night sweats. On the day of admission, he had vomiting and diarrhea, felt acutely unwell, and collapsed. In the emergency room he was febrile (temperature, 39.4°C) and unresponsive, with a Glasgow coma scale of 5–7. A fine erythematous rash was noted over his chest, and the examining physician believed that he had meningismus. CT imaging of his head was normal, and the initial lumbar puncture revealed clear CSF with a glucose of 4.1 mM (serum glucose, 7.1 mM); protein, 455 mg/L (450 mg/L, upper limit of normal); erythrocytes, 6 erythrocytes/L; and leukocytes, <1 × 10⁶ leukocytes/L. His level of consciousness fluctuated; he electively underwent intubation to protect his airway and was admitted to the intensive care unit. Collateral history revealed that he was working in and around a barn on a goat farm during the month before admission. He was empirically treated with ceftriaxone and doxycycline. He initially demonstrated fluctuating levels of consciousness, with mild hyperreflexia and increased tone in his lower extremities. Investigations including electroencephalography and MRI of the brain, cervical, and thoracic spine did not reveal any abnormalities. Cultures of the CSF, throat washings, blood, and stool were negative for bacteria and viruses. He was diagnosed with acute Q fever after a 4-fold increase in the antibody titer to the phase II antigen of *C. burnetii* was demonstrated (table 1). His symptoms improved, and he was discharged home to complete a 10-day course of doxycycline treatment.
At follow-up 1 month later, he had persistent complaints of debilitating fatigue, hypersomnolence, sweats, problems with memory and concentration, and vague sensory complaints in his legs. Clinically, he had no focal neurologic deficit, and subsequent electromyelography studies were normal. Neuropsychologic testing revealed mild, generalized cognitive impairment. Although these symptoms persisted over the next 6 months, he remained afebrile even during episodes of sweats. Repeated neuropsychologic testing in November showed mild general improvement in cognitive efficiency. In December 1999, he was admitted to the hospital with severe abdominal pain that was believed to be related to the abdominal wall musculature; this resolved with conservative treatment. An ultrasound of the abdomen revealed findings consistent with a fatty liver. He was readmitted in January for similar abdominal pain. He was afebrile, with a normal leukocyte count (5.0 × 10^9 leukocytes/L) and a mild reduction in his platelet count (9140/microL), with a normal glucose level of 4.3 mg/L, and he had normal liver function tests (alanine aminotransferase, 184 IU/L [41 IU/L, upper limit of normal]; aspartate aminotransferase [AST], 161 IU/L [42 IU/L, upper limit of normal]). An ultrasound and CT of the abdomen demonstrated findings consistent with fatty liver, with 2 small cysts in the right lobe, and subsequent CT performed in November showed mild improvement in his abdominal pain but continued to have sweats, fatigue, and cognitive complaints.

Table 1. Antibody titers to phase I and phase II Coxiella burnetii antigens (indirect immunofluorescence assay) for patient 1.

<table>
<thead>
<tr>
<th>Date</th>
<th>Phase I antibody titer</th>
<th>Phase II antibody titer</th>
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<tbody>
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<td>1:8</td>
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<td>1:4096</td>
</tr>
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<td>30 December 1999</td>
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Although repeat MRI of his head revealed only some thickening of the paranasal sinuses, a repeat lumbar puncture was performed to investigate his persistent cognitive complaints. This study showed substantially increased CSF protein of 1101 mg/L, with a normal glucose level of 4.3 mM and a WBC count of 7 × 10^6 cells/L (53% lymphocytes, 11% monocytes, and 36% neutrophils). Cultures of the CSF were negative for bacteria, and fungi and C. burnetii DNA could not be identified in his CSF by use of PCR.

A diagnosis of chronic Q fever was made, and treatment was started with ciprofloxacin and rifampin. At follow-up 6 weeks later, he had mild improvement in his abdominal pain but continued to have sweats, fatigue, and cognitive complaints.

Follow-up serological examination showed improvement, with the phase I titer decreasing to 1:256.

Patient 2. This 53-year-old woman developed acute onset of a nonspecific febrile illness associated with severe headaches, neck stiffness, fever, chills, myalgias, fatigue, cough, and shortness of breath around 10 March 1999. Investigations at that time revealed a normal leukocyte count and mild increase of lactic dehydrogenase (LDH) 144 U/L (115 U/L, upper limit of normal) and AST 28 U/L (26 U/L, upper limit of normal). Six days before presentation with this illness, she underwent coronary angiography and percutaneous transcatheter angioptoplasty (PTCA) of a stenotic lesion in her right coronary artery (without placement of a coronary stent). Her symptoms resolved over the course of the next 6 weeks without specific therapy.

In April 1999, her daughter, who was working on a goat farm, was diagnosed with Q fever during an epidemiologic investigation of acute Q fever among goat workers in a newly formed goat-farming cooperative [17]. She developed a constellation of symptoms including fever, chills, headache, myalgias, fatigue, neck stiffness, cough, and sputum 3 weeks before her mother’s illness. The index patient lived with her daughter, and, although she did not visit the farm, our patient frequently washed her daughter’s soiled clothing. Subsequent testing in May 1999 revealed an antibody titer to phase II C. burnetii antigen of <1:4096 and a phase I antibody titer of 1:64, suggesting that she had been recently infected with C. burnetii. She was treated with a 2-week course of doxycycline.

In September 1999, follow-up serological examination revealed that the patient’s antibody titer to phase I had increased to 1:1024. Although she was asymptomatic, she had serologic evidence of chronic Q fever. A transthoracic echocardiogram did not reveal any evidence of endocarditis. However, a chest radiograph taken in June revealed an opacity in the right upper lobe, and subsequent CT performed in November showed sev-

Table 2. Serological testing of patient 2 for Q fever.

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<tr>
<th>Date</th>
<th>Phase I antibody titer</th>
<th>Phase II antibody titer</th>
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<td>7 May 1999</td>
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<td>28 January 2000</td>
<td>1:128</td>
<td>1:256</td>
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eral very small pulmonary parenchymal foci bilaterally in both lungs.

It was believed that the focus of chronic C. burnetii infection was endovascular and probably related to her PTCA. She was started on therapy in August 1999 with ciprofloxacin 750 mg orally b.i.d. and rifampin 600 mg orally q.d., with subsequent testing showing a decline in the C. burnetii antibody titers (table 2).

**Patient 3.** In December 1995, this 66-year-old man with a history of aorto-bifemoral bypass grafts for peripheral vascular disease developed daily episodes of fevers, chills, and night sweats. After development of an acutely swollen left leg, he was admitted to hospital for assessment. Ultrasound of his leg did not reveal any evidence of venous thrombosis; however, he was mildly leukopenic and anemic (WBC count, 4.5 × 10^9 cells/L; hemoglobin, 119 g/L). While in the hospital, he became pancytopenic and had mild increases in his liver enzymes (AST, 71 IU/L [29 IU/L, upper limit of normal]; alkaline phosphatase, 192 IU/L [104 IU/L, upper limit of normal]) and lipase (500 IU/L [upper limit of normal, 200 IU/L]).

Bone marrow biopsy showed slightly generalized hyperplasia with no evidence of malignancy. A biopsy of his liver was described as a lymphocytic infiltrate but had no evidence of changes consistent with Q fever. A CT scan of his abdomen revealed a horseshoe-shaped kidney, a previous aortic graft for peripheral vascular disease, a simple hepatic cyst, and a possible pancreatic mass; however, laparotomy and subsequent biopsy of the pancreas revealed some loss of fat cells and a marginal reaction composed of lymphocytes and histiocytes that was suggestive of an inflammatory process, but there was no evidence of a tumor. His postoperative course was complicated by esophageal candidiasis and *Pseudomonas aeruginosa* nosocomial pneumonia. All other cultures of blood urine and sputum were negative for bacteria and mycobacteria. Serum immunoglobulin levels were normal, with a small IgG κ biclonal protein. Colonoscopy revealed a small polyp, and rectal biopsies for amyloid were negative. Other investigations included anti–nuclear antibody, thyroid-stimulating hormone, α fetal protein, carcinoembryonic antigen, hepatitis B surface antigen, bone marrow biopsy showed slightly generalized hyperplasia with no evidence of malignancy. A biopsy of his liver was described as a lymphocytic infiltrate but had no evidence of changes consistent with Q fever. A CT scan of his abdomen revealed a horseshoe-shaped kidney, a previous aortic graft for peripheral vascular disease, a simple hepatic cyst, and a possible pancreatic mass; however, laparotomy and subsequent biopsy of the pancreas revealed some loss of fat cells and a marginal reaction composed of lymphocytes and histiocytes that was suggestive of an inflammatory process, but there was no evidence of a tumor. His postoperative course was complicated by esophageal candidiasis and *Pseudomonas aeruginosa* nosocomial pneumonia. All other cultures of blood urine and sputum were negative for bacteria and mycobacteria. Serum immunoglobulin levels were normal, with a small IgG κ biclonal protein. Colonoscopy revealed a small polyp, and rectal biopsies for amyloid were negative. Other investigations included anti–nuclear antibody, thyroid-stimulating hormone, α fetal protein, carcinoembryonic antigen, hepatitis B surface antigen, antibody response is directed primarily against phase II antigen, whereas in chronic infections the predominant response is directed against phase I [22, 26]. An IgG antibody titer of at least 1:800 to phase I antigen as measured by indirect immunofluorescence is diagnostic of chronic Q fever [23]. Conversely, an IgG antibody titer of <1:400 to phase I antigen has a negative predictive value for chronic Q fever of 100% [27].

**DISCUSSION**

Because of the fastidious nature and special growth requirements of *C. burnetii*, routine culture is not feasible. Diagnosis is commonly made by demonstrating seroconversion in the appropriate clinical setting [24]. *C. burnetii* has 2 distinct antigenic presentations, or phases. In nature, *C. burnetii* expresses phase I antigen. After many passages through tissue culture, the microorganism undergoes a phase variation and expresses phase II antigen [25]. During acute infection in humans, the antibody response is directed primarily against phase II antigen, whereas in chronic infections the predominant response is directed against phase I [22, 26]. An IgG antibody titer of at least 1:800 to phase I antigen as measured by indirect immunofluorescence is diagnostic of chronic Q fever [23]. Conversely, an IgG antibody titer of <1:400 to phase I antigen has a negative predictive value for chronic Q fever of 100% [27].

**Chronic Q fever is uncommon. Before 1989 there were only 234 reports in the literature [28]. The most common manifestation of chronic *C. burnetii* infection is culture-negative endocarditis, which accounts for 60%–70% of all chronic cases of Q fever [23, 29]. Brouqui et al. [29] proposed that chronic **Table 3. Serological testing of patient 3 for Q fever.**

<table>
<thead>
<tr>
<th>Date</th>
<th>Phase I antibody titer</th>
<th>Phase II antibody titer</th>
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</tr>
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<td>18 July 1997</td>
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Q fever be classified into 3 subgroups: (1) Q-fever endocarditis, (2) chronic Q fever with underlying heart or vascular disease but no evidence of endocarditis, and (3) chronic Q fever without cardiovascular involvement.

In this article, we present 3 patients with atypical manifestations of chronic Q fever. These patients had a diagnosis of chronic *C. burnetii* infection made on the basis of a high phase I antibody titer. Our first patient had persistent vague neurologic complaints after being treated for acute Q-fever meningitis. Neurologic manifestations of acute Q fever are uncommon but date back to World War II and may include primary infection (meningitis and encephalitis) and symptoms as a result of embolic phenomena secondary to Q-fever endocarditis [30–32]. Signs and symptoms vary and can include extrapyramidal symptoms, aphasia, ataxia, weakness, seizures, decreased visual acuity, diplopia, disorientation, hallucinations, and behavioral disturbances [27, 32]. Symptoms usually resolve with treatment; however, occasionally the patient may be left with a persistent neurologic deficit [23, 32]. To our knowledge there has not been a case of primary chronic *C. burnetii* CNS infection reported in the literature. Repeat serological testing for Q fever in our first patient was diagnostic of chronic Q fever, and although it is difficult to attribute many of his nonspecific symptoms to chronic Q fever, his CSF picture is consistent with ongoing inflammation.

In addition to his neurologic findings, he also had mild increases in his liver enzymes and a radiologic picture of a fatty liver. Marrie [33] suggests that Q-fever hepatitis can manifest in 1 of 3 ways: an infectious hepatitis-like picture, increases in liver enzymes as an incidental finding in a person with acute Q fever, and granulomatous hepatitis presenting as a fever of unknown origin. Mild increases are commonly found in patients with Q fever, and hepatitis is usually an acute manifestation. Chronic forms of the disease have been described and are usually associated with concurrent endocarditis, but isolated hepatitis has been documented [21, 29, 34]. Mononuclear cell infiltration of the portal tracts, focal necrosis, and fatty changes have all been described pathologic changes of Q-fever hepatitis. Classically, *C. burnetii* infections of the liver are characterized by doughnut granulomas, which consist of a dense fibrin ring surrounded by a central lipid vacuole. However, these pathologic findings are nonspecific and can be seen in Hodgkin’s disease, infectious mononucleosis, and leishmaniasis [33, 35, 36]. Our patient’s liver biopsy revealed mild steatosis and no evidence of granulomatous liver inflammation.

The lack of documented ongoing fever seen in the first case is not unusual. Despite its name, fever may be absent in some cases of chronic Q fever. Fournier et al. [37] found that 6 (46%) of 13 patients with *C. burnetii* vascular infection did not have temperatures of >38°C. Similarly, fever was absent from 32% of patients diagnosed with Q-fever endocarditis [23]. Our patient’s normal ESR is more unusual, because chronic Q fever is typically accompanied by an ongoing inflammatory response characterized by an increased ESR [23, 29, 33, 35]. Although there was some initial improvement in his chronic symptoms with treatment, he remained significantly fatigued. Other investigators have documented persistent fatigue associated with *C. burnetii* infection [23, 38, 39].

Our last 2 patients would fit into the second category outlined by Brouqui et al. [29]: chronic Q fever with underlying heart or vascular disease but no evidence of endocarditis. Although the initial febrile illness resolved in our second patient, her antibody titer of to phase I antigen subsequently increased to 1:1024. Around the time of her acute infection, she underwent cardiac angiography and angioplasty for coronary artery disease. Brouqui et al. [29] reported a case of a patient who had *C. burnetii* isolated from the blood and who presented with fever after undergoing coronary artery dilatation. It is possible that the endovascular trauma experienced by our patient as a result of angioplasty was the inciting event that established a chronic endovascular infection. Chronic infections of other endovascular structures, such as aortic aneurysms and vascular prosthesis, have been reported [29, 37]. The other potential focus of chronic Q fever in this patient is her small pulmonary nodules. Pulmonary fibrosis and pseudotumors of the lung are rare pulmonary manifestations of Q fever [23, 40, 41]. Pseudotumors typically present as solitary lesions on chest radiography and are often mistaken for a malignant mass [40, 41]. Our patient, however, had multiple small pulmonary parenchymal foci rather than a single lesion.

The manifestation of chronic Q fever in our third patient is unclear. The etiology of his acute presentation was never found; however, rarely, acute Q fever can present as acute pancreatitis [23], and the histopathology of this man’s pancreatic biopsy was suggestive of an inflammatory process. Unfortunately, we do not have a serum sample from that admission to look for serologic evidence of acute Q fever. Although the original liver biopsy did not reveal any evidence of *C. burnetii* infection, his persistently increased liver enzymes suggest that the liver is a possible site of infection, but unfortunately he did not go on to have a biopsy of his liver. The other possible focus for infection to consider would be his prosthetic aorto-bifemoral graft. Fournier et al. [37] reviewed 13 cases of chronic *C. burnetii* infections of aneurysms and vascular grafts, including 2 patients with aorto-bifemoral grafts. Both patients had serological results diagnostic of chronic Q fever and had *C. burnetii* cultured from graft samples removed as part of therapy. Although our patient had a history of aorto-bifemoral bypass grafts for peripheral vascular disease, his gallium scan did not reveal any evidence of ongoing infection.

Chronic *C. burnetii* infection often goes undiagnosed and usually depends on the interest of local physicians and the avail-
ability of special diagnostic tests [37]. The most common manifestation of chronic Q fever is culture-negative endocarditis, but atypical manifestations can occur. Chronic Q fever should be considered in patients presenting with an unexplained febrile illness or persistent systemic inflammatory states who have an underlying history of heart or vascular disease, particularly if they have a history of exposure to farm animals or other high-risk animals, such as cats.

Several methods other than serological testing are available for the diagnosis of Q fever. Culture of *C. burnetii* can be performed by using a shell-vial technique with human embryonic fibroblast cells, but this must be done in a biosafety level 3 laboratory [42]. PCR can be used to amplify *C. burnetii* DNA from a variety of tissues [42]. Several genes have been used to generate specific primers, including 16S ribosomal RNA, 23S rDNA, superoxide dismutase, plasmid based sequences, and the IS1111 multicopy insertion sequence [42]. However, most important is a consideration of the diagnosis of Q fever—once that occurs, the diagnosis can be confirmed by serological testing, culture, or PCR.

References