Q fever endocarditis: A case report and review of the literature

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The case of a 31-year-old man from Alberta diagnosed with Q fever endocarditis is presented. To the authors' knowledge, this is the first case of Q fever endocarditis diagnosed in the province of Alberta. The patient had undergone open valvulotomy for congenital aortic stenosis as an infant. He presented with congestive heart failure secondary to severe aortic regurgitation and underwent mechanical aortic valve replacement. Early failure of the mechanical prosthesis and numerous laboratory abnormalities prompted an investigation for endocarditis, which was initially negative. Markedly positive serology eventually established the diagnosis of chronic Q fever. The patient subsequently underwent a second aortic valve replacement following initiation of appropriate antimicrobials directed against *Coxiella burnetii*. The present report reviews the clinical presentation and diagnosis of Q fever endocarditis. It highlights the insidious and nonspecific nature of the presenting symptoms, and emphasizes the use of serology for diagnosis. Increased awareness and earlier diagnosis can significantly decrease the morbidity and mortality associated with this disease.

Key Words: *Coxiella burnetii*; Endocarditis; Q Fever

Endocarditis is the most common presentation of chronic Q fever, a zoonosis caused by the obligate intracellular bacteria *Coxiella burnetii*. Commonly believed to be a rare disorder, it has been estimated to account for up to 5% of all endocarditis cases worldwide (1-3). It occurs almost exclusively in patients who have pre-existing valvular disease or who are immunocompromised (4). Unlike typical cases of endocarditis, the clinical presentation of chronic Q fever is often nonspecific. Furthermore, specialized techniques are required for identification of the organism, and echocardiographic evidence of infection is frequently absent (5). Without prompt recognition and appropriate antimicrobial therapy, the course of Q fever endocarditis is severe and potentially fatal. The following case demonstrates many of the clinical features of chronic Q fever and highlights the difficulty of obtaining the diagnosis.

CASE PRESENTATION

A 31-year-old Caucasian man presented to a walk-in clinic complaining of progressive, exertional shortness of breath. He had moved to Calgary, Alberta, from Nova Scotia, where he had worked on a dairy farm, two years prior. Due to pre-existing

L'endocardite de la fièvre Q : Rapport de cas et analyse bibliographique

Le cas d'un Albertain de 31 ans obtenant un diagnostic d'endocardite de la fièvre Q est exposé. En autant que le sache l'auteur, c'est le premier cas d'endocardite de la fièvre Q à être diagnostiqué dans la province de l'Alberta. Lorsqu'il était nourrisson, le patient a subi une valvulotomie ouverte en raison d'une sténose aortique congénitale. Il a consulté parce qu'il souffrait d'insuffisance cardiaque congestive secondaire à une régurgitation aortique marquée. Il a subi un remplacement valvulaire mécanique de l'aorte. Un échec rapide de la prothèse mécanique et de nombreuses anomalies de laboratoire ont suscité une exploration d'endocardite, qui s'est d'abord révélée négative. Une sérologie manifestement positive a fini par permettre d'établir le diagnostic de fièvre Q chronique. Le patient a subi un deuxième remplacement valvulaire aortique après l'application d'un traitement antimicrobien orienté contre le *Coxiella burnetii*. Le présent rapport analyse la présentation clinique et le diagnostic d'endocardite de la fièvre. Il souligne la nature insidieuse et non spécifique des manifestations initiales ainsi que l'utilisation de la sérologie pour poser le diagnostic. Une meilleure sensibilisation et un diagnostic plus précoce peuvent réduire considérablement la morbidité et la mortalité associées à cette maladie.

congenital valvular heart disease, he was referred to the Adult Congenital Cardiology Clinic at the University of Calgary (Calgary, Alberta). The patient could barely climb one flight of stairs without significant shortness of breath, and had developed orthopnea and paroxysmal nocturnal dyspnea. He described occasional palpitations, but denied any syncopal episodes, chest discomfort or peripheral edema. There were no symptoms suggestive of systemic infection.

Of note, the patient had been diagnosed with congenital aortic stenosis at the age of eight months and underwent open aortic valvulotomy. The patient was found to have a trileaflet valve with significant fusion of the leaflets. Catheterization at the age of 10 years revealed a peak residual gradient of 25 mmHg across the aortic valve with mild aortic insufficiency. Echocardiograms at the ages of 18 and 22 years demonstrated peak gradients of 37 mmHg and 56 mmHg, respectively, moderate aortic insufficiency and preserved left ventricular function. The patient had no cardiology follow-up after the age of 22 years.

Physical examination revealed a blood pressure of 110/50 mmHg, a heart rate of 82 beats/min and a normal

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oxygen saturation on room air. He was cachectic and had severe acne. No peripheral stigmata of endocarditis were found. Bounding pulses were evident along with a positive Durozier's sign. The patient's jugular venous pressure was normal. Auscultation revealed a single S2, as well as an S3. He had a grade 4 of 6 systolic ejection murmur at the base, with a long, grade 3 of 6, high-pitched, diastolic murmur best heard along the left lower sternal border. The patient's lungs were clear on auscultation. No peripheral edema was evident. Mild hepatosplenomegaly was noted.

The electrocardiogram showed an incomplete left bundle branch block and left ventricular hypertrophy with nonspecific repolarization abnormalities. A transthoracic echocardiogram showed a dilated left ventricle (end-systolic and end-diastolic dimensions of 74 mm and 51 mm, respectively) with normal systolic function. There was mild aortic stenosis with a peak gradient of 48 mmHg, but severe aortic regurgitation (grade 4+) and a peak right ventricular systolic pressure of 55 mmHg. No vegetations were identified. A magnetic resonance imaging scan revealed normal origins of both coronaries but slight dilation of the left coronary artery. The aortic root was normal. Cardiac catheterization revealed an ejection fraction of 41%, left ventricular end-diastolic pressure of 29 mmHg, severe aortic regurgitation, mild aortic stenosis and normal coronary arteries.

The patient was noted to have a number of laboratory abnormalities, including mild normocytic anemia (hemoglobin 110 g/L; mean corpuscular volume 87 fL), mild lymphocytosis (3.7×10^9 cells/L) and moderate neutropenia (1.1×10^9 cells/L). Iron studies were consistent with anemia of chronic disease. A peripheral smear revealed atypical lymphocytes, which were subsequently deemed to be reactive on the basis of a normal bone marrow biopsy. Blood cultures were consistently negative, though his erythrocyte sedimentation rate (ESR) was elevated (63 mm; normal range 0 mm to 10 mm). Further testing revealed liver enzyme abnormalities, with an alkaline phosphatase concentration of 154 U/L (normal 30 U/L to 145 U/L) and an alanine aminotransferase concentration of 99 U/L (normal 1 U/L to 60 U/L). Serum protein electrophoresis was notable for increased gamma globulins consisting of several monoclonal bands. An extensive workup, including consultation with the Department of Internal Medicine and Infectious Diseases, revealed no identifiable cause, and Q fever was not suspected at that time. These findings were attributed to severe aortic insufficiency and subsequent 'cardiac cachexia'.

The patient was referred to the Congenital Cardiovascular Surgery service at the University of Alberta (Edmonton, Alberta). At surgery, the ascending aorta was dilated at 57 mm, but the sinotubular junction and aortic sinuses appeared normal. The aortic valve, subaortic area and anterior mitral valve leaflets looked as though they had previously been affected by endocarditis. There was a deep aneurysm of the perimembranous intraventricular septum consistent with a healed abscess cavity. There were no signs of active infection. Microscopy and cultures of operative specimens revealed no microorganisms. Pathological examination of the resected aortic valve specimen reported marked nodular fibrosis and calcification. He underwent aortic valve replacement with a 29 mm St Jude mechanical aortic prosthesis (St Jude Medical Inc, USA), replacement of the ascending aorta with a 30 mm Hemashield graft (Boston Scientific, USA), suture repair of an anterior mitral valve leaflet perforation, and repair of the perimembranous aneurysm of the intraventricular septum.

Follow-up at three months after surgery found the patient feeling well, but examination unexpectedly revealed a grade 3 of 6 diastolic murmur. A transthoracic echocardiogram confirmed a moderate to severe paravalvular leak, which, with persistent lymphocytosis, prompted a repeat infectious disease consultation. Eight sets of blood cultures were obtained and incubated for 21 days. All were negative. Additionally, serology for *Brucella* species and *Legionella* species was negative. The cardiac surgeon, who had previously practiced in Nova Scotia, became suspicious that this could be a case of Q fever endocarditis and prompted serology for *Coxiella* species to be sent as well. The patient was treated empirically with ciprofloxacin and rifampin, given his province of origin and the appearance of his valve at the time of his surgery. Serology for Q fever was delayed due to the concurrent severe acute respiratory syndrome epidemic and the subsequent demands on the provincial microbiological laboratory.

Due to the severity of his cardiac symptoms, the patient underwent urgent surgery, including repeat aortic root replacement with a 25 mm homograft valve, replacement of the ascending aorta with an aortic homograft and repair of the left ventricular outflow tract aneurysm. Intraoperatively, they found the aortic graft to be encased in thick fibrotic tissue. Histological examination of the valve revealed valvulitis but no vegetations. Special histological stains for microorganisms were negative. Repeated electron microscopy studies failed to show any *Coxiella* species organisms. Shortly after the operation, the patient's *Coxiella* species serology returned. The phase I antigen had a titre of 1:131,072, and the phase II titre was 1:65,536, consistent with a diagnosis of chronic Q fever. The valve tissue was subsequently sent to the research laboratory of Dr D Raoult in Marseilles, France, where *C burnetii* was isolated from the valve using special culture techniques.

The patient had a complicated postoperative course, including a right lateral thoracotomy for empyema. He was discharged from hospital six weeks after his second aortic valve replacement. Follow-up at one, three, six and 12 months found the patient doing well, with no evidence of systemic infection and a normal-appearing and normal-functioning aortic valve prosthesis.

DISCUSSION

Q fever is a ubiquitous infection and has been reported worldwide. There are some areas that appear to have a preponderance for the disease, such as the Basque region of Spain and the south of France (4). Domestic ruminants (cattle, goats and sheep) form the major reservoir for *C burnetii*. However, domestic cats and dogs may also be reservoirs, as highlighted in a number of outbreak investigations (6,7). Humans are infected by the inhalation of aerosolized organisms following exposure to infected fomites or products of conception. The acute form of Q fever typically presents as a nonspecific febrile illness, acute hepatitis or atypical pneumonia; however, as many as 60% of cases are asymptomatic (4).

Of particular relevance in Canada, Nova Scotia has a particularly high prevalence of *C burnetii* infection, which was first revealed when acute Q fever was found to be a common cause of atypical pneumonia in the province (8). Subsequently, 174 cases were reported by Marrie (9) between 1980 and 1987. Furthermore, 11 cases of Q fever endocarditis were reported in the province from 1979 to 2003 (10). It has been estimated that *C burnetii* is the etiological agent in approximately 3% of

TABLE 1
Clinical and laboratory manifestations of chronic Q fever

Variable	Cases (%)
Clinical features	
Male sex	72
Exposure to domestic ruminants	56
Known valvulopathy	96
Fever	85
Heart failure	54
Hepatomegaly	48
Splenomegaly	36
Purpuric rash	14
Arterial embolism	30
Laboratory features	
Increased erythrocyte sedimentation rate	71
Anemia	49
Thrombocytopenia	36
Increased alanine and aspartate aminotransferases	32
Increased alkaline phosphatase	27

Data from references 5 and 37 to 40

all cases of endocarditis in Nova Scotia (3). Cases of Q fever have also been reported in other provinces, including Ontario, Quebec, Newfoundland, New Brunswick and Prince Edward Island (11-16). Seropositivity of more than 15% of blood donors in Manitoba indicated that unrecognized Q fever may also be present in western Canada (15). To date, no previous case of Q fever has been reported in the province of Alberta.

While acute Q fever is common, only a very small proportion of individuals develop chronic infection, which usually manifests as endocarditis. In a cohort of 1569 patients from France diagnosed with acute Q fever, only 12 individuals developed endocarditis (17). Chronic infection occurs almost exclusively in two groups: those with pre-existing valvular heart disease and those who are immunocompromised (18,19). In one recent series, patients with a valvulopathy and acute Q fever had a 38.7% chance of going on to develop endocarditis (17). Patients with valvular prostheses are at the greatest risk (19). The median time to development of chronic Q fever was six months following acute infection, although a latent period of up to 20 years has been reported (20). Men account for the majority of cases (75% in one review [5]), no doubt due to the influence of occupational exposure. Among cases in the immunocompromised population, active malignancy is the biggest risk factor for developing Q fever endocarditis. Whether the malignancy itself or its treatment predisposes to chronic infection is unknown (21). Additionally, numerous cases of endocarditis have been observed in individuals infected with HIV (22).

The clinical presentation of chronic Q fever is insidious and lacks many of the typical features of subacute, bacterial endocarditis. As a result, there is often a significant delay in diagnosis. Despite increasing awareness, recent studies demonstrate a mean delay of seven months from symptom onset to diagnosis (5). The majority of cases present with congestive heart failure due to valvular dysfunction (5). Unlike typical cases of endocarditis, fever is absent in a significant proportion and is frequently intermittent or low grade (17). Although embolic phenomena have been reported in up to one-third of cases, these are usually limited to advanced disease (23). Immune complex glomerulonephritis is frequent and usually

TABLE 2
Serological diagnosis of Q fever

Diagnosis	Phase I antibody titre	Phase II antibody titre	Sensitivity (%)	Specificity (%)
Unlikely Q fever	—	IgG≤1:100	—	—
Acute Q fever	—	IgG≥1:200	81.9	96.1
		IgM≥1:50	67.2	98.8
Chronic Q fever	IgG≥1:800	—	100.0	99.6

Ig Immunoglobulin

manifests as microscopic hematuria (24). A purpuric rash can also be found in a minority of patients (5).

There are many peripheral manifestations of Q fever endocarditis that can provide essential clues as to the diagnosis. Specifically, hepatomegaly and splenomegaly are evident on physical examination in up to one-half of cases (4). Mild hepatitis is usually seen concurrently on biochemical analysis, with elevation of both aminotransferases and alkaline phosphatase. Furthermore, a systemic inflammatory syndrome is seen in most patients, manifested in part by a significantly elevated ESR (18). Many hematological abnormalities are also observed in up to 50% of cases, with the most frequent being anemia (5). Less commonly observed abnormalities include leukocytosis, leukopenia and thrombocytopenia. A recent report noted that many of the clinical and biochemical abnormalities noted above are absent earlier in the course of chronic Q fever (5). Specifically, the incidence of hematological abnormalities and elevated ESRs were significantly reduced in cases diagnosed within a mean of six months, compared with cases diagnosed at a mean of 18 months. The clinical and laboratory findings of chronic Q fever are summarized in Table 1.

Echocardiography, usually the mainstay of diagnostic imaging in endocarditis, is of limited value in chronic Q fever. In fact, transthoracic echocardiography reveals abnormalities in only 12% of cases (4). This is due, in large part, to the small size and nodular shape of the typical vegetations (25). While transesophageal echocardiography is far superior in demonstrating lesions, it too has significant limitations. In a recent series, only five of 15 cases had vegetations visible on transesophageal echocardiography, and a further case had a visible abscess (5).

The diagnosis of Q fever endocarditis is hampered by the inability to culture *C burnetii* using routine media. As a strict obligate intracellular bacterium, it can only be cultured in living cell lines, most commonly using the shell vial method (26). However, the lack of sensitivity and cumbersome nature of current culture methods has largely limited their use to research laboratories. The diagnosis of chronic Q fever, therefore, relies on serological testing (Table 2). Chronic Q fever is characterized by increased titres against the phase I antigen. An immunoglobulin G anti-phase I antibody titre of 1:800 or greater has a specificity of 99.6% for the diagnosis of chronic Q fever (27,28). In fact, the Duke criteria (29) have been modified to include this serological cutoff as a major criterion for the diagnosis of endocarditis.

The gold standard for the diagnosis of infective endocarditis remains the pathological demonstration of organisms on the heart valve. Here too, the diagnosis of Q fever endocarditis remains challenging. In a recent series, only 18% of cases showed the typical histological features of endocarditis, specifically, vegetations, inflammatory infiltrates and significant

tissue destruction (30). More commonly, only extensive fibrosis and calcification were evident, which were difficult to discern from degenerative changes. *C burnetii* itself is not visible within macrophages on routine hematoxylin and eosin staining, and even special staining is unlikely to reveal the organism. Immunohistochemistry and polymerase chain reaction are more successful in demonstrating the presence of the organism; however, polymerase chain reaction has a sensitivity of only 75% (30).

The clinical course of Q fever endocarditis is often severe. The mortality among cases reported before 1987 was 37% (5). The poor prognosis is believed to be due, in large part, to significant delays in diagnosis, which postpone appropriate antimicrobial therapy. This is supported by a recent series in which a mortality rate of only 10% was observed in cases diagnosed a mean of six months after presentation (5).

The optimal treatment of Q fever endocarditis has not been completely defined, in part due to the difficulty of its culture and the inapplicability of conventional antibiotic susceptibility assays. In vitro studies, using chronically infected cell cultures (which better mimic the conditions of chronic Q fever), have shown doxycycline, chloramphenicol, rifampin and quinolones to be active against *C burnetii* (31,32). Whether these antibiotics are truly bactericidal or simply bacteriostatic depends on the cell culture model used. In the model developed by Raoult et al (32), only doxycycline in combination with chloroquine exhibited bactericidal activity. Data regarding clinical outcomes with respect to various antibiotic regimens consist mainly of case series and nonrandomized studies. Combination therapy using two antibiotics active against *C burnetii* in vitro appear to be successful. Specifically, the combination of a fluoroquinolone with either doxycycline or rifampin were successful in controlling infection, although

relapse rates were as high as 50% at discontinuation despite prolonged therapy of up to three years (33,34). More recently, the combination of doxycycline and chloroquine was compared with doxycycline and ofloxacin in a nonrandomized, nonblinded study (35). The doxycycline and chloroquine group experienced markedly fewer relapses; in fact, no relapses were observed after 18 months of treatment. The results of this report indicate that doxycycline and hydroxychloroquine may be the preferred treatment for chronic Q fever.

Regardless of the treatment regimen, close clinical monitoring is required. First, given the insidious nature of the disease, patients should have phase I serology checked at regular intervals to ensure efficacy of the regimen. A phase I immunoglobulin G titre of less than 1:200 has been proposed as the main criterion for a clinical cure (36). Similarly, due to the high relapse rate after discontinuation of antibiotics, patients should be followed closely with clinical assessment, echocardiography and laboratory investigation, including phase I serology, at regular intervals (4).

CONCLUSION

Q fever endocarditis lacks many of the usual clinical and echocardiographic features common to typical cases of endocarditis. As such, the diagnosis is often significantly delayed or even missed, resulting in significant morbidity and mortality. The systemic features of chronic Q fever can provide essential clues as to the presence of *Coxiella* species infection. However, it is imperative that physicians maintain a high index of suspicion, especially among patients with valvular disease and those who are immunocompromised. Serological testing for *Coxiella* species provides rapid and accurate diagnosis of chronic Q fever, allowing for prompt initiation of appropriate antimicrobial therapy and improved clinical outcomes.

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