Endocarditis After Acute Q Fever in Patients with Previously Undiagnosed Valvulopathies

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We describe 3 cases of endocarditis after acute Q fever in 3 patients with clinically silent, undiagnosed valvulopathies, including mitral valve prolapse, minimal valvular leak, and bicuspid aortic valve. We conclude that, to prevent endocarditis, these minor valvulopathies must be actively searched for with echocardiography after diagnosis of acute Q fever.

Q fever is a zoonosis caused by Coxiella burnetii [1]. In humans, infection results primarily from the inhalation of contaminated aerosols [1]. This organism is highly infectious and has been considered as a potential agent of warfare [2]. The diagnosis of Q fever relies mainly on serological techniques [1]. The disease is divided into acute and chronic infections, which evolve differently clinically, have distinct serological profiles, and require different treatments [1]. Acute Q fever represents primary infection with C. burnetii. It is asymptomatic in 60% of cases. In the remaining 40%, it is usually mild and is sometimes complicated by febrile illness, pneumonia, or hepatitis infection. Chronic Q fever subsequently develops in patients with predisposing factors. Patients with valvulopathies are at risk of developing Q fever endocarditis [3]. No presentation of acute Q fever is more predictive than another of whether chronic disease will develop and what its severity will be. Symptoms of Q fever endocarditis are often nonspecific, which explains the often-delayed diagnosis. The presence of unexplained inflammatory disease with valvulopathy in persons with increased risk of exposure to Q fever, mainly those who have had contact with farm animals, suggests the possibility of Q fever endocarditis, and such patients should be systematically checked.

In a previous study, some of us and our colleagues described the transformation from acute disease to endocarditis during a follow up of 12 patients with identified valvulopathies [4]. We estimated this risk of transformation to be ~40% [4]. The usual treatment regimen of doxycycline (200 mg per day for 3 weeks) for acute Q fever was not sufficient to prevent the occurrence of endocarditis in patients with acute Q fever and valvulopathy. A combination of doxycycline (200 mg per day) plus hydroxychloroquine (600 mg per day) for 12 months seemed to be more effective [4]. We suggested that patients with acute Q fever and valvulopathy should be treated using this regimen or receive follow-up serological examination.

However, when an existing valvulopathy is not recognized at the time of acute Q fever diagnosis, it is difficult to propose a specific treatment for these patients. We describe 3 cases of patients with clinically silent valvulopathy at the time that they received a diagnosis of acute Q fever who later developed endocarditis.

**Case 1.** A 45-year-old male physician was hospitalized in November 2003 for dyspnea. His medical history included acute Q fever that had been diagnosed in May 1998. He had hepatitis infection, and his serological profile was typical of acute Q fever (titers of antibodies to phase II IgG [anti–phase II IgG], 1:200; titers of anti–phase II IgM, 1:200). No cardiac murmur was noted. He was treated with doxycycline (200 mg per day for 3 weeks). He did not exhibit any symptoms of infection after treatment. In November 2003, he presented with dyspnea without fever. Findings of clinical examination revealed the presence of a murmur due to aortic insufficiency. Transesophageal echocardiography showed an aortic insufficiency with a bicuspid aortic valve. Blood culture performed on usual medium were negative. Serological tests for Q fever showed a profile typical of Q fever endocarditis (titers of anti–phase I IgG, 1:25,600; titers of antibodies to phase I IgM [anti–phase I IgM], 0; titers of anti–phase I IgA, 1:400). Treatment based on doxycycline (200 mg per day) and hydroxychloroquine (600 mg per day) was started. Because of the severity of the patient’s aortic insufficiency, he underwent valvular replacement. Histological examination of the valve specimen showed polymorphonuclear cells and inflammatory lesions, and C. burnetii was identified by immunochemical examination with a monoclonal antibody (figure 1) [5]. PCR and culture of the valve specimen were positive for C. burnetii. At present, the patient remains healthy.
Figure 1. Histological examination of a cardiac valve specimen from patient 1. Top, Note the extensive fibrosis of the connective valve tissue and the mononuclear inflammatory cell infiltrate composed mainly of macrophages (hematoxylin-eosin-saffron stain; original magnification, ×40). Center, Focal and small inflammatory infiltrates with immunostained macrophages (arrow), representing a small area in the whole valve tissue surface. The valve stroma* is reorganized and fibrotic (immunoperoxidase staining with an anti-CD68 monoclonal antibody; original magnification, ×40). Bottom, Immunohistochemical detection of *Coxiella burnetii* in a resected cardiac valve with a monoclonal antibody and hematoxylin counterstain. Note the intracellular location of the bacteria in the macrophage cytoplasm (arrow) (original magnification, ×400).
**Case 2.** A 53-year-old woman presented in July 2003 with hepatitis infection. The diagnosis of acute Q fever was made on the basis of the patient’s serological profile (titers of anti-phase II IgG, 1:800; titers of anti-phase II IgM, 1:50). The patient recovered after treatment with doxycycline (200 mg per day for 3 weeks). No particular medical history was noticed. In September 2003, she presented with fever. Transesophageal echocardiography showed a mitral valve prolapse and mitral valve vegetations. Blood cultures performed on usual medium were negative. Serological examination showed a profile typical of Q fever endocarditis (titers of anti-phase II IgG, 1:3200; titers of anti-phase II IgM, 1:1600). The patient recovered after treatment with doxycycline (200 mg per day for 3 weeks). No particular medical history was noticed. Transesophageal echocardiography was performed. No abnormality was noted. In February 2005, he presented with fever. Transesophageal echocardiography revealed a trivial mitral valve insufficiency and a mitral valve vegetation. Blood cultures were negative for C. burnetii. Diagnosis of Q fever endocarditis was made on the basis of serological examination findings (titers of anti-phase I IgG, 1:1600; titers of anti-phase I IgM, 1:400; titers of anti-phase I IgA, 0). Treatment based on doxycycline (200 mg per day) and hydroxychloroquine (600 mg per day) was started. At present, the patient remains healthy.

**Case 3.** A 50-year-old man presented in July 2004 with hepatitis infection. The diagnosis of acute Q fever was made on the basis of a typical serological profile (titers of anti-phase II IgG, 0; titers of anti-phase II IgM, 1:1600). The patient recovered after treatment with doxycycline (200 mg per day for 3 weeks). No particular medical history was noticed. Transesophageal echocardiography was performed. No abnormality was noted. In February 2005, he presented with fever. Transesophageal echocardiography revealed a trivial mitral valve insufficiency and a mitral valve vegetation. Blood cultures were negative for C. burnetii. Diagnosis of Q fever endocarditis was made on the basis of the patient’s serum sample was positive for C. burnetii [6]. Treatment based on doxycycline (200 mg per day) and hydroxychloroquine (600 mg per day) was started in February 2005. At present, the patient remains healthy.

**Conclusions.** We report 3 cases of transformation from acute Q fever to endocarditis in patients with unknown valvulopathies at the time acute Q fever was diagnosed. These observations confirm that minor valvulopathies, such as minor valvular insufficiency, mitral valve prolapse, and bicuspid aortic valve, are predisposing factors for endocarditis in patients with acute Q fever [7–9]. They also demonstrate that it is critical to diagnose these valvulopathies in patients with acute Q fever. However, these valvulopathies may go undetected throughout the patient’s lifetime, because they are difficult to diagnose using only cardiac auscultation [10, 11]. The use of transthoracic echocardiography usually leads to the discovery of these valvulopathies [10, 11]; however, they may still be missed. For example, a patient who was cared for by one of us (D.R.) first received a diagnosis of Q fever endocarditis in a previously normal aortic valve with inconclusive transthoracic echocardiography findings. However, during surgery, a bicuspid aortic valve was discovered. Another patient who consulted one of us (D.R.) did not receive a diagnosis of bicuspid aortic valve with transthoracic echocardiography, but the diagnosis was made after transesophageal echocardiography (D.R., unpublished data).

The difficulty of diagnosing mitral valve prolapse and bicuspid aortic valve has been heightened recently. Hayek et al. [12] have concluded that echocardiography is the method of choice for diagnosing mitral valve prolapse. Moreover, transthoracic echocardiography may not adequately visualize the entire mitral valve, which may sometimes lead to a misdiagnosis, whereas transesophageal echocardiography is very effective in identifying prolapsing segments [12]. Lewin et al. [13] have reported that, with transthoracic echocardiography, bicuspid aortic valve can be misleading because of poor visualization, and transesophageal imaging may be necessary for the accurate evaluation of valve anatomy. Finally, if we consider the series of 92 patients with Q fever endocarditis described by Palmer et al. [14], only one-third of the patients were noted to have an underlying heart valve lesion predisposing them to Q fever endocarditis. We speculate that this low rate is linked to an underdiagnosis of minor valvulopathies.

Because Q fever endocarditis is associated with substantial morbidity and mortality, and antibiotic prophylaxis has been shown to be an effective measure, it is necessary to optimize the diagnosis of valvulopathies in patients with acute Q fever. When valvulopathies are present, a follow-up plan should be implemented, because the disease may progress insidiously, as it did for patient 1. The sole manifestation of endocarditis in this patient was an acute cardiac insufficiency 5 years after an episode of acute Q fever. No second episode of fever was observed. The necessary emergency valve replacement could have been prevented with adequate management. On the basis of these observations, we now propose for all patients with a diagnosis of acute Q fever that, at the very least, transthoracic echocardiography should be performed to detect valvulopathies. It is important to underline that there are groups of people at risk for whom valvulopathy should definitely be excluded with transesophageal echocardiography, if necessary. These groups are patients >60 years in age and those with a relative who has an aortic valve anomaly. Indeed, a significant number of people aged >60 years have undetected valve disease, and an inherited component to the etiology of bicuspid aortic valve has been recently confirmed [15].

A specific treatment or follow-up serological examination (every 3 months for at least 2 years) should be performed for all patients with acute Q fever and valvulopathy. The serological method used for this follow up is important. The best tool is the analysis of antibodies against the phase I antigen of C. burnetii with an immunofluorescence assay. However, this antigen is not available on the usual commercialized tests, because the production of phase I antigen is difficult and requires competence at performing animal inoculation in a biosafety level...
Only scientists in reference laboratories could obtain an accurate diagnosis of chronic Q fever. Two markers, IL-10 and TNF, could be tested parallel to serological examination, because it has been demonstrated that the production of these 2 markers were enhanced in patients who developed Q fever endocarditis [16]. Tests for lymphocytopenia could also be done, because the presence of lymphocytopenia that involves mainly CD4+ T cells has been reported in patients with Q fever endocarditis [17].

We now recommend that transthoracic echocardiography should be systematically performed for all patients with acute Q fever to detect valvulopathy to improve the management of the disease.

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References