Changing Clinical Presentation of Q Fever Endocarditis

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Fifteen cases of Q fever endocarditis that occurred in 1999–2000 in southern France are described and compared with 15 cases from the same area reported in 1987. Significant decreases were found in the prevalences of heart failure, hepatomegaly, inflammatory syndrome, anemia, leukopenia, and abnormal liver function test results in patients who had Q fever endocarditis after 1997. This was probably the result of a reduction in the delay before diagnosis of the disease and of the use of novel, effective antibiotic regimens.

Q fever is a ubiquitous zoonosis caused by Coxiella burnetii, an obligate intracellular bacteria. The natural reservoirs of the organism are mainly cattle, goats, and sheep. Infections in humans can be acute or chronic. Chronic Q fever presents mainly as endocarditis, and 5% of the patients with endocarditis in France have the disease. Q fever endocarditis occurs almost exclusively in patients who have had a previous cardiac valve defect or in immunocompromised patients [1]. Because many possible clinical manifestations of Q fever endocarditis exist, most of which are nonspecific, the diagnosis of the disease, which is currently made on the basis of the results of serologic testing, is often delayed for several months [2].

An increase in interest in Q fever has been observed in several countries, and the resultant heightened awareness of the disease among doctors has led to earlier diagnoses. Presently, the recognized clinical signs of Q fever endocarditis are based on descriptions of patients in whom diagnoses have been delayed, so these clinical signs are actually the signs of the disease in its later stages. However, the signs of Q fever endocarditis may be different in the earlier stages of the disease [2, 3]. Also, improvements in the antibiotic treatment regimens for Q fever endocarditis and the more careful follow-up of patients have led to changes in the prognosis for persons with the disease [1].

We describe patients who had Q fever endocarditis diagnosed by our laboratory in 1999–2000, and we compare our findings with those for 15 patients from the same area with Q fever endocarditis reported in 1987. Also, our cases and others described in 1997–2000 are compared with cases reported in 1967–1987.

Patients. Our laboratory, located in Marseille, France, is the French National Reference Center for rickettsial diseases, and it receives serum samples from most French hospitals for Q fever serologic testing. In this study, the diagnosis of Q fever endocarditis was made by use of the modified Duke criteria, which includes a ratio of IgG antibody titer to phase 1 antigen of ≥1:800 as a major criterion [1]. Patients who had Q fever endocarditis diagnosed in 1999–2000 were included in our study, and their doctors were asked to provide additional serum samples, blood or tissue samples for culture, and epidemiologic, clinical, and laboratory data. Transequophageal echocardiography was performed on all patients in the study.

The indirect immunofluorescent antibody test was used to determine titers of IgG, IgM, and IgA to both phase 1 and phase 2 C. burnetii antigens. For the isolation of C. burnetii, specimens of heparinized blood and homogenized cardiac valves were inoculated onto human embryonic lung cells in shell vials, as reported elsewhere [1]. Growth of the bacteria was detected by use of immunofluorescence testing. Bacterial DNA was detected in surgically excised valves by use of a C. burnetii–specific pair of primers that amplified an htpAB-associated repetitive element [1].

By use of Epi Info, version 6 (Centers for Disease Control and Prevention), we compared the epidemiologic, clinical, echocardiographic, and biologic data for our patients with data reported in 1987 from a similar study in our area [4]. Data from our patients and from patients described elsewhere in 1997–2000 were compared with data from a series of Q fever endocarditis cases described in 1967–1987. Qualitative data were compared by use of Fisher’s exact test, and mean values were compared by use of Student’s t test. A difference was considered statistically significant at P < .05.

Results. In 1999 and 2000, Q fever endocarditis was diagnosed in 15 patients, 13 of whom were men. The average age of the patients was 60 years (range, 32–79 years). Fourteen patients had a history of exposure to domestic ruminants, which are known reservoirs of C. burnetii, and 10 lived in rural areas. Patients were hospitalized in Marseille (11 patients), Lyon...
Table 1. Comparison of clinical, echocardiographic, and biologic data for patients with Q fever endocarditis from 5 recent and 7 earlier studies.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Study or studies</th>
<th>P value</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Raoult et al. [4]</td>
<td>Total from 7 earlier studies [4–10]</td>
<td>Present study</td>
<td>Total from 5 recent studies [2, 3, 11, 12]</td>
</tr>
<tr>
<td>Patients</td>
<td>15</td>
<td>76</td>
<td>15</td>
<td>97</td>
</tr>
<tr>
<td>Men</td>
<td>9</td>
<td>57 (76)</td>
<td>13</td>
<td>68 (70)</td>
</tr>
<tr>
<td>Exposure to domestic ruminants</td>
<td>6</td>
<td>45 (59)</td>
<td>14</td>
<td>45/90 (50)</td>
</tr>
<tr>
<td>Known valvulopathy</td>
<td>15</td>
<td>76 (100)</td>
<td>14</td>
<td>93 (96)</td>
</tr>
<tr>
<td>Mitral valve</td>
<td>7</td>
<td>24 (32)</td>
<td>7</td>
<td>26 (27)</td>
</tr>
<tr>
<td>Aortic valve</td>
<td>5</td>
<td>39 (51)</td>
<td>5</td>
<td>38 (39)</td>
</tr>
<tr>
<td>Mitral and aortic valves</td>
<td>3</td>
<td>13 (17)</td>
<td>2</td>
<td>27 (28)</td>
</tr>
<tr>
<td>Symptom at presentation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>11</td>
<td>51 (67)</td>
<td>10</td>
<td>79/90 (88)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>9</td>
<td>30/47 (64)</td>
<td>3</td>
<td>54/90 (60)</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>12</td>
<td>44 (58)</td>
<td>5</td>
<td>44/88 (50)</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>7</td>
<td>43 (57)</td>
<td>4</td>
<td>33/88 (38)</td>
</tr>
<tr>
<td>Digital clubbing</td>
<td>2</td>
<td>28 (37)</td>
<td>3</td>
<td>9/49 (18)</td>
</tr>
<tr>
<td>Purpuric rash</td>
<td>2</td>
<td>16 (21)</td>
<td>1</td>
<td>11/70 (16)</td>
</tr>
<tr>
<td>Arterial embolism</td>
<td>2</td>
<td>17 (22)</td>
<td>4</td>
<td>21/69 (30)</td>
</tr>
<tr>
<td>Biologic data</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased γ-globulin level</td>
<td>15</td>
<td>58/62 (94)</td>
<td>3/4</td>
<td>16/18 (89)</td>
</tr>
<tr>
<td>Increased ESR</td>
<td>15</td>
<td>65/74 (88)</td>
<td>8</td>
<td>64/87 (74)</td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>5</td>
<td>—</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>6</td>
<td>—</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>Anemia</td>
<td>13</td>
<td>44 (58)</td>
<td>6</td>
<td>31/61 (51)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>7</td>
<td>30/45 (67)</td>
<td>6</td>
<td>20/57 (35)</td>
</tr>
<tr>
<td>Increased SGOT/SGPT level</td>
<td>7/11</td>
<td>25/30 (83)</td>
<td>3</td>
<td>21/59 (36)</td>
</tr>
<tr>
<td>Increased AP level</td>
<td>11</td>
<td>35/44 (80)</td>
<td>2/12</td>
<td>11/36 (31)</td>
</tr>
<tr>
<td>Receipt of surgical treatment</td>
<td>7</td>
<td>—</td>
<td>10</td>
<td>59 (61)</td>
</tr>
<tr>
<td>Death</td>
<td>6</td>
<td>28 (37)</td>
<td>0</td>
<td>16 (16)</td>
</tr>
<tr>
<td>Delay in diagnosis, mean months</td>
<td>18</td>
<td>12</td>
<td>6</td>
<td>7</td>
</tr>
</tbody>
</table>

NOTE. Data are no. (%) of patients or no. of patients with the characteristic/total no. of patients for whom data were available (%), unless otherwise indicated. AP, alkaline phosphatase; ESR, erythrocyte sedimentation rate; SGOT, serum aspartate aminotransferase; SGPT, serum alanine aminotransferase.
The general laboratory data are presented in table 1. An increased erythrocyte sedimentation rate (ESR) was found in 8 patients; WBC counts were normal in all patients, except for 1 patient who had leukopenia (leukocyte count, \(<4 \times 10^9\) leukocytes/L). Anemia and thrombocytopenia were present in 6 patients, and 3 patients had abnormal findings of liver function tests. Two of 4 patients had positive results of latex tests for rheumatoid factor.

All patients had high IgG antibody titers to both phase 1 and phase 2 antigens, and 9 had high IgA antibody titers to phase 1 antigen. C. burnetii was cultured from the blood samples obtained from 2 of 12 patients; the organism was isolated from the valves of 7 of 10 patients. In these 7 patients, DNA of C. burnetii was detected by PCR in the samples of their heart valves that were submitted. For 1 patient, who had received 18 months of treatment before valve resection, the culture of the valve specimen was negative, but C. burnetii DNA was detected by PCR. Of the 2 valves for which results of PCR and culture were negative, one was resected before treatment and the other was resected after 4 months of antibiotic treatment.

All patients were treated with antibiotics. Before specific diagnoses were made, 2 patients were given a combination of \(\beta\)-lactams and aminoglycosides, and 1 patient received a combination of a \(\beta\)-lactam and a fluoroquinolone. The infections did not respond to these regimens. Once Q fever endocarditis had been diagnosed, all patients received and benefited from continuous treatment with doxycycline plus hydroxychloroquine. Nine patients had undergone valve replacement after the onset of their endocarditis, 5 of whom underwent it after starting specific therapy. The indication for cardiac surgery was hemodynamic failure in 3 patients and embolic phenomena in 3 other patients; in the 3 latter patients, surgical indications were severe mitral regurgitation (1 patient), a dehiscent prosthesis (1 patient), and a valvular abscess (1 patient). To date, patients have been receiving treatment for 3–27 months and are still being treated as of this writing.

Discussion. Q fever endocarditis is not an uncommon disease; \(>800\) cases were reported from 1949 through 2000 [1]. These reports have led to a heightened awareness of the disease among doctors, and the result—earlier diagnosis of Q fever endocarditis—has been suggested to be responsible for changes in the clinical presentation of the disease [3]. To assess this hypothesis, we compared the findings from our series of patients with those reported for 15 patients from the same area described in the older study (4 of 15 cases vs. 12 of 15 cases; \(P<.005\)), in which patients frequently had undergone several valve replacements before Q fever endocarditis was diagnosed. Subsequent studies have shown that most of these replacements were related to valve destruction caused by C. burnetii before Q fever was diagnosed [1]. Although the majority of patients in the earlier study experienced heart failure and/or hepatomegaly, only one-fifth and one-third of the patients in our study had these signs, respectively.

In a similar comparative study by Boyle and Hone [3], a reduction in the rate of hepatomegaly was also found, but this finding was not significant. In the patients in our study, increased ESR, abnormal WBC counts, anemia, and increased alkaline phosphatase activities occurred significantly less frequently than they did in the earlier study (table 1). High levels of anti–phase 1 IgA antibodies were found in 14 patients in the earlier study, whereas we found only 9 patients with high IgA titers (\(P<.05\)). Since 1994, however, it has been known that IgA titers to phase 1 are not diagnostic for chronic Q fever [1]. When the data for the 97 patients from our study and other recent studies published in 1997–2000 [2, 3, 11, 12] were compared with the data from 76 patients reported in 1967–1987 [4–10], we found a significantly higher prevalence of hepatomegaly, digital clubbing, increased ESR, thrombocytopenia, and increased liver enzyme activities in the patients described in the earlier studies (table 1).

Boyle and Hone [3] also found a lower prevalence of thrombocytopenia in patients who had recent cases of Q fever endocarditis and suggested that the apparent changes in the presentation of patients with chronic Q fever endocarditis may reflect a decrease in the mean delay in diagnosis of the disease. The mean delay was 6 months in our study, compared with 18 months in the previous French report [4]. Also, there was a significant decrease in the diagnostic delay in the series of 97 recent cases we compiled, as compared with the 76 earlier cases. The shortened diagnostic delay may be a result of a heightened awareness among doctors of C. burnetii being a possible cause of endocarditis, which likely resulted in doctors obtaining more appropriate patient histories. This is supported by our finding that, in the histories of 14 of the 15 patients we studied, a record of exposure to domestic ruminants existed, whereas such exposure was reported in only 6 of 15 patients in the earlier French study.

In addition, as a result of the diagnoses having been made.
earlier, there were significantly fewer inappropriate antimicrobial therapies used in our study than there were in the previous report from our area (3 vs. 13 patients; $P<.01$). Moreover, the usefulness of echocardiography in the diagnosis of Q fever endocarditis appears to have improved with the transesophageal approach, because valve lesions were found in 13 of 15 patients in our study but in only 8 of 15 patients in the earlier French study ($P = \text{NS}$). Because visceral involvement occurs late in the course of disease, Q fever endocarditis can easily be missed in its early stage [1]. Therefore, it should be emphasized that an unexplained illness in a patient with an existing heart valve lesion is a strong indicator of Q fever. In such patients, serologic testing for Q fever and transesophageal echocardiography should be performed routinely so that the diagnosis can be confirmed by use of the modified Duke criteria [1]. By use of these methods, we observed, for the first time, the occurrence of endocarditis in 3 patients with a preexisting valvulopathy who presented with acute Q fever. The median time to development of endocarditis was 4 months.

The treatment recommended for Q fever endocarditis has recently been changed to the combined use of doxycycline and hydroxychloroquine [1]. All 15 patients in our study received this regimen, and no patients died. By comparison, in the earlier French study, in which the majority of patients were treated with a tetracycline alone, 6 of 15 patients died [4]. A similar improvement in the mortality rates was observed when we compared the data we compiled on recent cases of Q fever endocarditis with the data on earlier cases. The mortality rate was 37% for the 76 patients described in the reports up to 1987, whereas, for the 97 patients described in 1997–2000, it was only 16% ($P<.005$). Again, although most patients in earlier reports were treated with tetracycline alone, combinations of doxycycline and other antimicrobials were the most common treatments used for the recently described patients. Of the 76 patients described from 1997–2000, 15 patients were treated with doxycycline and hydroxychloroquine, 14 were treated with doxycycline and trimethoprim-sulfamethoxazole, 9 were treated with doxycycline and a fluoroquinolone, 5 were treated with doxycycline and rifampin, 22 were treated with doxycycline only, and 7 were treated with other or changing regimens of antimicrobials [3, 11, 12]. Thus, it would appear that the new antibiotic regimens and the earlier initiation of treatment have improved the prognosis for chronic Q fever endocarditis, even though they do not appear to alter the need for surgical replacement of affected valves.

Our results suggest that a heightened awareness among doctors of Q fever endocarditis and its treatment, coupled with improved diagnostic methods for the disease (mainly serologic testing and echocardiography), likely resulted in the significant changes in the characteristics of Q fever endocarditis that have occurred in the past 2 decades. This has also been reported for other infectious diseases after the introduction of new medical practices or social and environmental changes [13]. It is important, then, that series of clinical cases of even well-known diseases continue to be reported and discussed, because this will help ensure the dissemination of the most up-to-date medical knowledge.

Acknowledgment

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References