Q FEVER AFTER A JOURNEY IN SYRIA: A DIAGNOSIS SUGGESTED BY BONE MARROW BIOPSY

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ABSTRACT

A Belgian patient developed Q fever after a journey in Syria. Coxiella burnetii infection was diagnosed because of the presence of granulomas with a central vacuole in a bone marrow biopsy. During doxycycline treatment all his symptoms disappeared.

INTRODUCTION

Fever after travelling to exotic countries is a frequent reason for consultation. Q fever is a relatively rare cause of “imported fever”, which is often diagnosed retrospectively, on the basis of serological tests. We report a case of Q fever after a journey in Syria, diagnosed when a bone marrow biopsy revealed the presence of vacuolated granulomas.

CASE REPORT

A 45-year-old Belgian archaeologist, with a medical history of multiple allergies, hepatitis A and typhoid fever, was admitted on June 22nd, 1998, with a fever, chills and myalgias of 3 weeks’ duration.

Over a period of 20 years, the patient travelled to Syria twice a year to do archaeological work. He returned to Belgium on May 16th, after a two-week visit to Syria. On June 2nd, a few hours after a dentist had performed a local anaesthesia for caries treatment, he developed a fever. As the fever and myalgias persisted during the following days, he visited his general practitioner. Treatment with cefuroxime-azetil was started because a dental abscess was suspected. After six days no clinical improvement was noted. The antibiotic treatment was stopped because of a maculopapular rash. No remission of symptoms had been observed under the prescribed treatment.

The patient was referred to our department two weeks later. On admission, physical examination revealed a temperature of 39 °C, but no other clinical abnormalities. Laboratory data showed a white blood cell count of 9400/mm³ (with 59.5% neutrophils and 24.5% lymphocytes), a sedimentation rate of 83 mm/h, a C reactive protein (CRP) of 20 mg/dl, and moderate hepatic tests alterations (GOT 115 U/l, GPT 136 U/l, GGT 87 U/l, alkaline phosphatase 119 U/l, LDH 1252 U/l, total bilirubin 0.9 mg/dl). Blood cultures did not reveal bacterial pathogens. A chest X-ray showed a minimal left paridiaphragmatic infiltrate. A tuberculin skin test was negative. Serological tests showed a past infection with hepatitis A and a possible reactivation of Epstein-Barr virus infection (IgG > 100 and IgM +). Serological tests for hepatitis B, C, E, Borrelia burgdorferi, Brucella abortus bovis, Human Immunodeficiency Virus, Leishmania and Entamoeba histolytica infection were all negative. Rheumatoid factor and antinuclear antibody were not detected, however, smooth-muscle autoantibodies were present (1/320). Serological results by complement fixation test for Mycoplasma pneumoniae, Chlamydia, Legionella, and Q fever were not interpretable because of an anti-complement activity of patient’s serum.

After one week of observation, the patient complained of left thoracic pain, increasing with deep inspiration. A transthoracic echocardiography revealed a mild pericardial effusion, but no valvular abnormality. A computerised tomography (CT) of the chest showed a small left pleural effusion and a minimal left parenchymal infiltrate. A bone marrow biopsy revealed granulomas with epitheloid histiocytes. These granulomas had a

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central clear vacuole, characteristic of a *Coxiella burnetii* infection (Figure 1).

Doxycycline was started, with progressive resolution of the inflammatory syndrome and the liver tests abnormalities, and complete disappearance of symptoms.

The diagnosis of acute Q fever was confirmed one week later, by a strong serological positivity for *C. burnetii* under indirect immunofluorescence (MRD diagnostics, Cypress, California, in Belgium distributed by Forlab, Brussels) (Table I).

**DISCUSSION**

Q fever is a zoonosis caused by *C. burnetii*, a small gram-negative bacterium, which is strictly intracellular when infecting its host. *C. burnetii* is no longer included in the *Rickettsia* genus, as there are so many phenotypic differences (1).

Q fever is endemic in many parts of the world. Q fever can also be acquired in Belgium and other European countries (2, 3). The reservoir for *C. burnetii*, includes mammals, birds and ticks. Infected animals are asymptomatic, and clinical illness occurs only in humans. The most common sources of infection are cattle, sheep and goats, which explains the higher prevalence of Q fever in rural areas. However suburban and urban outbreaks have been reported, through transport of infected flocks (4), or exposure to other contaminated animals, such as dogs or cats, especially at times of parturition (5). Prevalence of Q fever varies widely according to the region, but reporting is also largely dependent on physicians' interest in the disease and on the existence of reliable laboratory facilities (6).

Infection in humans most often occurs after inhalation of aerosolised organisms or ingestion of unpasteurized milk. *C. burnetii* has a spore-like life cycle, so that it can withstand drying and remain viable for several years. Indirect infections are also possible through contact with dust from farm vehicles, contaminated laundry, and urban use of manure. Transmissions during laboratory procedures, or after participation in autopsies on infected patients are regularly reported (7).

Contamination of our patient probably occurred in Syria, in one of the remote rural places where he had been in contact with local dogs. The incubation period for Q fever is 2 to 6 weeks, which is exactly the time in which our patient had returned from Syria. The acute onset of symptoms just after the dental treatment was probably coincidental.

*C. burnetii* is extremely infectious for humans, and a single viable organism is enough to cause an infection (8). Clinical manifestations only occur in 50% of the infected individuals, and very few patients need hospitalisation. Clinical syndromes vary from a self-limiting flu-like syndrome, to a chronic life-threatening endocarditis. Acute Q fever usually presents as a mild febrile illness resolving in 1 to 2 weeks, or as an atypical pneumonia; Q fever is a classical cause of a community-acquired pneumonia, but with wide differences in prevalence according to the region (9). A posteriori, our patient reported that one of his colleagues in Syria had been repatriated to Europe for an atypical pneumonia. Clinical hepatitis is frequent in some regions (Spain, France), but usually, as in our patient, liver involvement is an incidental laboratory finding. Rare but classical complications of acute Q fever are meningoencephalitis (1%) and pericarditis either associated with myocarditis or not. It is worth noting here that our patient developed his typical pleuroperticardial pain after an isolated fever of one-month's duration. Finally, the transient maculopapular rash the patient had attributed to an allergic reaction was probably another symptom of *C. burnetii* infection, as observed in 20% of patients (7).

Chronic infections occur in probably less than 1% of infected patients (9), and the most frequent clinical

| Table 1 — Q fever indirect immunofluorescence antibody test: IgM AND IgG titres |
|---------------------------------|--------|--------|
| Titre to phase I antigen        | IgM    | IgG    |
|                                 | 1/512  | 1/512  |
| Titre to phase II antigen       | 1/4096 | 1/16384|

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presentation is an endocarditis (60-70%). There is always a previous valvular heart disease or an immunosuppressive condition. Other sites of infection are possible, such as vascular prostheses, aneurysms and bone. In general, clinical pictures are atypical and diagnoses are often delayed. The prevalence of Q fever has been reported to be 13 times higher and is more frequently symptomatic among HIV-infected patients than in the general population (10).

The diagnosis of Q fever can be suspected clinically, if there is an obvious recent exposure. Laboratory abnormalities include increased inflammatory parameters but with a normal white blood cell count and a slight elevation of the hepatic transaminase levels. Smooth-muscle auto-antibodies are found in 2/3 of patients, as well as other auto-antibodies, often in association with Q fever hepatitis (11). Chest X-rays often show minimal lung involvement, even in patients without pulmonary symptoms. Liver biopsies may reveal non-specific granuloma or granuloma with “doughnut appearance”. This typical central lipid vacuole surrounded by inflammatory cells and fibrin is characteristic of Q fever (12). The same histological appearance can be found in a bone marrow biopsy (13), as was observed in our patient.

Serology is the most convenient and the most commonly used diagnostic tool. Three methods are available: complement fixation (CF), indirect immunofluorescence antibody test (IFA) and enzyme-linked immunoassay (ELISA). CF is most widely used but lacks sensitivity (78%). In our patient, because of the presence of anti-complement activity of the patient’s serum, the CF serological results were not interpretable. ELISA and IFA are both highly sensitive and specific. The only observed cross-reaction with IFA involves Bartonella spp (6). During acute infection, host control of the disease is associated with an antibody response directed mainly at phase II antigen. Antibody formation to phase II antigen begins soon after infection with IgM responses within a few days and IgG responses occurring soon thereafter. Diagnosis can be easily made with a single sample if titres of IgG are > 1/200 and titres of IgM > 1/50. The presence of IgG to phase II antigen is indicative of acute disease. The presence of IgG to phase I antigen is indicative of chronic disease. During the acute phase, the IgM titres to phase II antigen are greater than those to phase I antigen. In the chronic disease, the IgM titres to phase I antigen are greater than or equal to phase II antigen. Chronic infections are characterised by the additional appearance of antibodies to phase I antigens (IgM, IgG) and a ratio of phase II to phase I antibodies < 1. The additional presence of IgA against phase I antibody is considered to be diagnostic for endocarditis (14). Genomic amplification (PCR) can be performed on biopsy specimens, especially cardiac valves, in cases of chronic infection. Cultures of C. burnetii can be obtained using a shell-vial assay, from different clinical specimens including blood (buffy-coat). Culture results may be obtained only after 14 days. In a recent study, blood cultures were found to be positive in 17% of patients with acute Q fever, often prior to seroconversion. On the other hand, 53% of patients with chronic Q fever had positive blood cultures (15).

Treatment guidelines for acute Q fever are based on experience but not on the results of clinical trials. The disease is often self-limiting, and when antibiotics are required a bacteriostatic effect seems to be sufficient. Tetracyclines are currently recommended for 2-3 weeks, but quinolone is another option, especially for the meningoencephalitis forms (16). Few data are available concerning other antibiotics. In our patient no clinical improvement was noted during cefuroxime-axetil treatment. Because of the presence of granulomas with a central clear vacuole in a bone marrow biopsy, doxycycline treatment was initiated before serological confirmation of Q fever was obtained. This treatment resulted in a rapid disappearance of the symptoms.

The treatment of Q fever endocarditis remains highly controversial. Antibiotic monotherapy is required for years and cannot prevent relapses after discontinuation. Various antibiotic combinations have been proposed, but apparently only the combination doxycycline-quinolone is able to decrease mortality. However, no cure was achieved after 2 years of treatment. Prolonged combined antibiotic therapy lasting at least 3 years is recommended, if possible until the disappearance of IgA against phase I antigen. Valve replacement should be reserved for cases of haemodynamic failure (14).

In conclusion, Q fever must be included in the differential diagnosis of prolonged fever in travellers and non-travellers, certainly when there is a history of a potential exposure. The presence of vacuolated granulomas in a bone marrow biopsy is pathognomonic for this infection.

ABSTRACT

Een Belgische patiënt ontwikkelt Q koorts na een verblijf in Syrië. De diagnose van Coxiella burnetii infectie werd gesteld wegens de aanwezigheid van granuloma met een centrale vacuole in een beenmerg biopsie. Onder doxycycline behandeling verdwenen alle symptomen.
REFERENCES