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Brief Report**Q-fever in a patient with a ventriculo-peritoneal drain****Case report and short review of the literature**P.J.F.M. Lohuis ^a, P.C. Ligtenberg ^a, R.J.A. Diepersloot ^b and M. de Graaf ^cDepartments of ^a Internal Medicine, ^b Microbiology and ^c Pulmonology, Diakonessen Hospital, Utrecht, Netherlands

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Although Q-fever is still a relatively rare disease in the Netherlands, its incidence seems to be increasing. In this article we describe the case-history of a 65-year-old woman with a Pudenz-drain, who acquired Q-fever pneumonia while manuring her garden. The course of the disease was deviant, which most likely was caused by colonization of the ventriculo-peritoneal drain with *Coxiella burnetii*.

Q-fever usually presents as a self-limiting illness. In the case of chronic Q-fever, complications such as endocarditis, hepatitis or meningo-encephalitis can be fatal and require long-term treatment. Patients with artificial drains or valves carry a greater risk of developing such complications. Therefore, especially in patients at risk, Q-fever should be included in the differential diagnosis when dealing with a patient with unexplained fever.

Key words: *Coxiella burnetii*; Q-fever; Ventriculo-peritoneal drain

Introduction

Q-fever, a zoonosis caused by the rickettsia *Coxiella burnetii*, was first described in 1937 and is now endemic in many parts of the world [1-3]. In the Netherlands it has been compulsory to report Q-fever to the Public Health authorities since January 1976. In 1991, 19 cases were reported [4]. This relatively low number might be explained by the fact that human infection is often mistaken for a viral illness and even runs an asymptomatic course [5]. Nevertheless, early diag-

nosis and treatment are of great importance in order to prevent serious complications such as endocarditis and meningo-encephalitis [6-8].

Because of the diagnostic problems we encountered in our patient and the amount of time that has passed since Q-fever was reviewed in the Netherlands, we present the case-history of a 65-year-old patient with Q-fever pneumonia.

Case Report

In April 1992 a 65-year-old woman was admitted to the Department of Lung Diseases at the Diakonessen Hospital in Utrecht, because of retrosternal pain. In 1986 she was operated on for a subarachnoidal bleeding for which she received a ventriculo-peritoneal drain. In 1991 she under-

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went cornea transplantation and hysterectomy. The patient was not known to have any heart disease.

Anamnestically, it appeared that while reading a book our patient became feverish and gradually developed a retrosternal pain, which at first stretched out to the ears and later on to the back. The pain appeared to be linked to respiration and increased in a lying posture. Nitroglycerine was administered by the general practitioner but afforded no relief. The patient did not cough and had no mucus production.

Physical examination disclosed a moderately ill woman, temperature 38.0°C, RR 160/80. Slight crepitations were heard over both lung bases. Heart tones were unremarkable as was the rest of the examination.

The chest-X-ray showed an increased heart size on the first day of admission, joined on the second day by a small infiltrate at the basal part of the right lung. Both ventilation/perfusion-scan and electrocardiogram appeared to be normal.

Laboratory investigations at admission: blood gas analysis revealed slight hypoxaemia, but no hyperventilation; ESR 20 mm/h (N 3–12), haemoglobin 8.0 mmol/l (N 7.6–9.6), WBC 6.4×10^9 (N 4.0–9.0) with a normal differential cell count, ASAT 11 U/l (N 0–25), ALAT 19 U/l (N 0–27) and CPK 66 U/l (N 0–110). Four weeks after admission these laboratory values had reached maximum levels: ESR increased to 95 mm/h, WBC to 12.8×10^9 , ASAT to 34 U/l and ALAT to 71 U/l. CRP was almost continuously increased with a highest value of 96 mg/l. Repeated blood cultures and liquor as well as urine and sputum cultures showed no growth.

On suspicion of a bacterial pneumonia, treatment with amoxicillin/clavulanic acid (1200 mg i.v., thrice daily) was started. In addition, a serum sample for virus serology was obtained. However, under this antibiotic treatment, the clinical situation deteriorated with weight loss, fatigue, nausea and persistent fever. Since the possibility of an atypical pneumonia was considered, antimicrobial treatment was then changed to erythromycin (500 mg orally, 4 times daily).

During treatment with erythromycin the patient remained febrile and still complained of retrosternal pain. Additional investigation was

performed to trace other possible foci. Consecutively gastroscopy, bronchoscopy, echography of the upper and lower abdomen, orthopantography and bone scintigraphy with Tc-MDP did not show any pathology.

Finally, 2 weeks after admission, the results of respiratory virus serology indicated a *Coxiella burnetii* infection. The complement fixing antibody titre rose from 1:4 to 1:128. Based on the diagnosis of Q-fever, treatment was then continued with doxycycline (100 mg i.v., twice daily) to which the patient clinically improved and became afebrile.

After 3 days her temperature rose again to 38.5°C. Transoesophageal echography (TEE) was then performed to exclude the presence of endocardial vegetations. In addition a CT-scan of the brain was performed because of the possibility of colonization of the ventriculo-peritoneal drain. Although both investigations failed to show any pathology, the possibility of chronic infection of the ventriculo-peritoneal drain was considered and we decided to treat the patient accordingly. In order to obtain satisfactory antibiotic concentrations in the cerebrospinal fluid, antibiotic treatment with chloramphenicol (1 g i.v., thrice daily and later 250 mg orally, twice daily) was started. Gradually temperature then dropped to normal values. Analysis of CSF after 12 days of chloramphenicol therapy did not show any abnormalities. Concentrations of chloramphenicol were not determined. TEE was repeated and excluded any valve pathology. After 2 months of hospitalisation our patient was discharged in good clinical condition. Because she did not tolerate oral chloramphenicol therapy she was then treated with doxycycline (100 mg orally, twice daily).

Three days after discharge the patient again became ill with fatigue, nausea, vomiting and a temperature of 38.2°C. The treatment was continued at the out-patient department with doxycycline (100 mg i.v., twice daily) but without any improvement. After 14 days treatment was therefore changed to ciprofloxacin (500 mg i.v., twice daily) on which the patient clinically improved. Ciprofloxacin therapy was stopped after 6 months. At that time no IgM antibodies to *Coxiella burnetii* were detectable, although she was still IgG-

positive for this pathogen. The patient has now been without symptoms for a follow-up of 6 months.

Discussion

Coxiella burnetii, a coccobacillus with a gram-negative cell wall, has been identified in a variety of arthropods and animals, but most commonly in cattle, sheep and goats [9,10]. Humans are infected by inhalation of contaminated aerosols, which can occur by direct or indirect contact with infected animals [11]. Examples of direct ways by which Q-fever may be acquired are exposure to parturient cats, skinned wild rabbits or slaughtered cattle [12]. However, indirectly, contamination can also occur through contaminated milk, manure, straw or dust from farm vehicles [13]. The latter way is most likely possible due to a spore stage of this micro-organism. This would explain its ability to withstand harsh environmental conditions, since it can survive for months in dried thick faeces, on wool, on fresh meat in cold storage, and in skimmed milk [5,10]. Transmission has been documented during an autopsy, but not during the clinical care of infected patients [14].

Although Q-fever may be asymptomatic, it usually presents as a self-limiting febrile illness. Symptoms seen most often include abrupt onset of high fever, severe frontal headache, shaking chills, anorexia, myalgia, nausea and non-productive cough. The incubation period of Q-fever varies from 14 to 39 days (with a mean of 20 days) and the entire course of the disease rarely exceeds 2 weeks [10]. Richardus et al. describe in a study of 33 patients that, apart from general symptoms, 54% of them had pneumonia (often with chest pain); 6% showed clinically manifest hepatitis and 9% developed endocarditis [15]. Neurological complications such as meningoencephalitis have also been reported [7,16]. Palmer claims in his study that Q-fever endocarditis accounts for approximately 3% of all cases of endocarditis reported [17]. Q-fever endocarditis is often fatal and typically occurs in persons with pre-existing valvular heart disease, prosthetic valves or vascular bypasses [6,17,18]. There might be a 5–10 year delay between acute infection and

diagnosis of chronic Q-fever endocarditis [8,17,19].

There are no specific haematological findings in patients with Q-fever [15]. A raised ESR and a moderate leukocytosis are often observed. Normochromic anaemia occurs in most severely ill patients. The differential blood count is usually normal. Generally, the cerebrospinal fluid shows no abnormalities.

Q-fever is diagnosed serologically. Indirect immunofluorescent reaction to IgM antibodies against *C. burnetii* is given preference to the complement fixation test, because of its greater sensitivity [15,20]. Since *C. burnetii* undergoes phase variation, a Phase I and a Phase II antigen can be distinguished. In humans only antibodies against Phase I antigen are found, unless the infection is chronic. A Phase II complement-fixing antibody titre greater than 1:32 is considered evidential for chronic Q-fever, although a Phase I complement-fixing antibody titre greater than 1:200 is also regarded as good evidence [6]. Peacock et al. suggest the possibility of differentiating between endocarditis and granulomatous hepatitis by using more specific serological methods. The presence of high Phase-I-specific IgA antibody titres in the indirect immunofluorescence test are diagnostic for endocarditis and adequately differentiates between these two entities of chronic Q-fever in humans [21]. Isolation of causative *C. burnetii* out of valvular tissue seems possible, but is tedious and involves a high risk of respiratory infections in laboratory workers [22].

Recognition of typical silhouettes on the chest-X-ray might be of diagnostic interest in the early onset of Q-fever. Chest film abnormalities in patients with Q-fever may resemble those seen with viral and *Mycoplasma pneumoniae* pneumonias in that they are characterized by patchy infiltrates. Chest X-ray abnormalities that have been reported include multiple, round, segmental opacities, linear atelectasis and complete partial lobar consolidation. Resolution of these lesions tended to be slow ranging from 10 to 70 days with an average of 30 days [23,24].

For years tetracycline drugs have been the antibiotics of choice when dealing with Q-fever.

Chloramphenicol, although equally effective, is less favoured because of the risk of aplastic anaemia. Co-trimoxazole is considered to be bactericidal against *C. burnetii* because the microbial metabolism is folate-dependent [25]. It has shown to be of additional advantage in combined therapy with doxycycline. The new quinolones were reported to be very active in vitro against *C. burnetii* [26]. Some anecdotal reports on successful treatment of confirmed cases of Q-fever have been documented in the literature recently [7,27–29].

In case of our patient the diagnosis of Q-fever was made after 14 days. Until the results of serology to respiratory viruses became available, treatment was based on the hypothesis of an atypical pneumonia. Infection with the microorganism most likely took place while the patient was manuring her garden with dried animal faeces. After Q-fever was diagnosed, antibiotic treatment with erythromycin was changed to doxycycline. On this treatment the patient became afebrile for only a few days, after which her temperature rose again. Possibly, potential vegetations on the ventriculo-peritoneal drain were only moderately reached by this antibiotic. Subsequent treatment with chloramphenicol, which is known to have better penetration of the blood-brain barrier, indeed caused a drop in temperature to normal levels. In addition, ESR, WBC and liver functions recovered. Shortly after discharge, our patient again became ill. Since oral doxycycline therapy appeared inadequate, treatment with ciprofloxacin (a quinolone) was started, on which the patient became afebrile. It is uncertain for how long this or any other antibiotic treatment should be continued. Relapses have been reported, even after several months of therapy and especially in patients with prosthetic valves or other vascular prostheses [18,22]. In some cases cure has been reported only after replacement of such a prosthesis. Thus, in the case of chronic Q-fever, antibiotic treatment should be continued for several months until no clinical evidence of infection is left and antibody titres measured by complement fixation are equal to or less than 128 [30]. When dealing with a patient carrying any artificial material which might

induce colonization with *C. burnetii*, replacement could be necessary to enable a cure.

Conclusion

As in many other countries, Q-fever now also seems to be endemic in the Netherlands. The true incidence of the disease might be significantly higher than documented, since many cases are either asymptomatic or mistaken for a viral illness. In the case of chronic Q-fever, complications such as hepatitis, endocarditis or meningoencephalitis can be fatal and require long-term treatment and follow-up. This case-report demonstrates that Q-fever should be included in the differential diagnosis when dealing with a patient with unexplained fever. Serological testing for *Coxiella burnetii* among other respiratory viruses should be performed in these patients. Patients with a vascular prosthesis or a ventriculo-peritoneal drain are at risk of developing vegetations with *C. burnetii* vegetations and require long-term treatment and follow-up. Replacement of the prosthesis should be considered in the process of treatment.

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