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Case Report

A case of giant cell arteritis associated with culture-proven *Coxiella burnetii* aortitis

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ABSTRACT

A case of proven *Coxiella burnetii* aortitis, possibly associated with giant cell arteritis (GCA), is reported. A 72-year-old man, who is a hunter, presented with weight loss, fever, jaw claudication, and hardened temporal arteries associated with a persistent inflammatory syndrome and arteritis of the whole aorta, including the brachiocephalic arteries, as seen on ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography. The diagnosis of GCA was retained, and treatment with prednisolone was started. Given the aneurysm of the abdominal aorta, the patient underwent replacement of the abdominal aorta with an allograft. Histology showed intense chronic arteritis attributed to atherosclerosis with dissection. However, *Coxiella burnetii* infection was confirmed by serology and then by culture and molecular biology on the surgical specimen. A combination of hydroxychloroquine and doxycycline was added to tapered prednisolone and the outcome was favourable.

1. Introduction

Q fever is a zoonosis caused by an obligate intracellular bacterium, *Coxiella burnetii*. The infection usually follows the inhalation of infected particles from cows, goats, sheep, cats, or dogs (Eldin et al., 2017). Acute Q fever (primary infection) is asymptomatic in about 20–80% of cases, or induces fever, a flu-like syndrome, pneumonia, or granulomatous hepatitis (Eldin et al., 2017).

Persistent focalized infections (endocarditis, vascular infections, pericarditis, osteoarticular infections, lymphadenitis, and genital infections) occur in 1–5% of patients. In France, endocarditis with negative blood cultures is the most frequent manifestation, followed by vascular prosthesis or aneurysm infections. However, in the Netherlands, vascular infections are diagnosed more frequently (Eldin et al., 2017). The diagnosis is difficult due to non-specific symptoms and relies on serology, PCR, and sometimes culture (Eldin et al., 2017).

Giant cell arteritis (GCA) is an inflammatory vasculitis of large- and medium-sized vessels, typically including one or several branches of the carotid, especially the temporal arteries. GCA can also involve other localizations such as the aorta. This systemic disease, affecting people older than 50 years, is most often characterized by headache, jaw claudication, fever, anaemia, and elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). The aetiology remains unclear, but several infectious diseases have been suspected as triggers of this deleterious immune reaction (Nagel et al., 2013; Nagel and Gilden, 2014).

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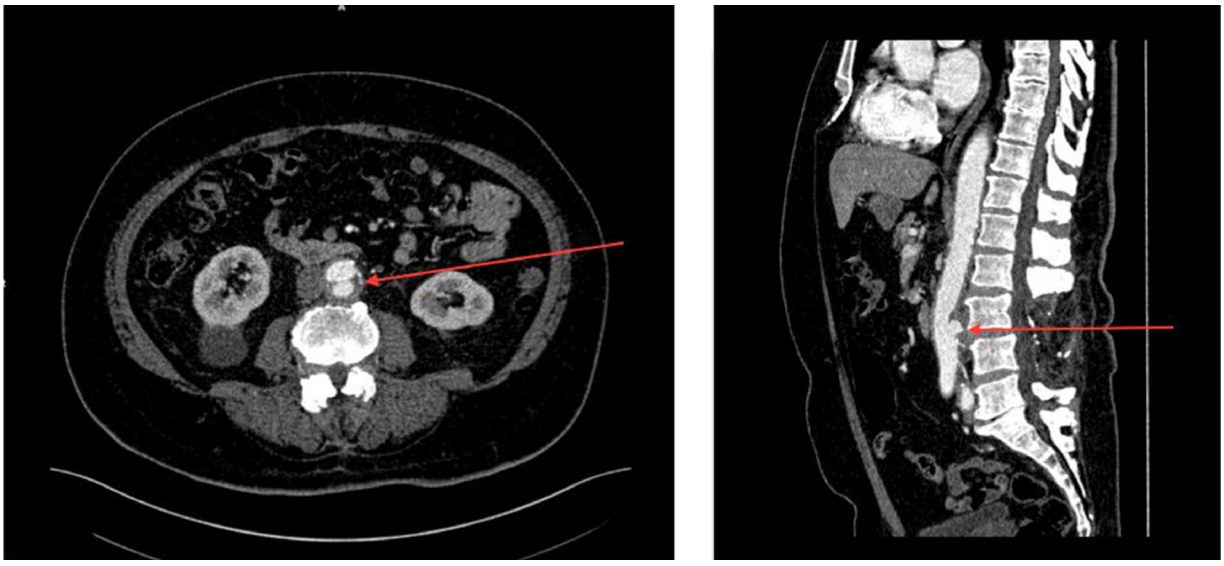

Figure 1. Abdominal CT showing thickening of the abdominal aorta walls and an aneurysm located on the posterior wall of the infrarenal aorta (red arrows). The cystic structure on the right kidney is a benign non-infectious cyst.

It appears that only two case reports showing an association between GCA and Q fever have been published previously (Lefebvre et al., 2010; Odeh and Oliven, 1994). Another study reported a patient who fulfilled the criteria for GCA, but this case was considered as 'Takayasu-like' aortitis associated with *C. burnetii* (Baziaka et al., 2014). A new case is presented here.

2. Case report

A 72-year-old man was hospitalized at the University Hospital of Liège in Belgium for the investigation of anorexia, weight loss of 13 kg, dyspnoea on exertion, asthenia, transit disorder, and possible jaw claudication with a duration of several months. Only one episode of fever (38 °C) was observed during the hospitalization. With the exception of bilaterally hardened temporal arteries, his physical examination was unremarkable. Chronic kidney disease, gout, one episode of urolithiasis, a gallbladder lithiasis, a phlebitis of the lower limbs complicated by pulmonary embolism, a vitreous haemorrhage, and idiopathic bilateral uveitis were noted in the patient's medical history. He was retired. He practiced hunting as a hobby and regularly consumed the flesh of game after having prepared it himself.

On admission, his haemoglobin was 10.9 g/dl, leukocyte count was 12.78×10^9/l with 77.8% polymorphonuclear neutrophils, and ESR was 75 mm/h. The CRP level ranged between 59.6 mg/l and 105 mg/l during his stay. He was negative for anti-neutrophil cytoplasmic antibodies (ANCA). Serology for hepatitis A and C viruses, HIV, Brucella, Bartonella, *Treponema pallidum*, *Francisella tularensis*, and Echinococcus were all negative, as were a QuantiFERON test and blood cultures for bacteria. An ultrasound of the temporal arteries performed before admission was normal. Fundoscopy was normal and the ventilation–perfusion (V/Q) scan did not show any abnormality. Transthoracic echocardiography (TTE) revealed a slightly lowered left ventricular ejection fraction (50%) and thickening of the free edge of the non-coronary cusp without dysfunction of the aortic or mitral leaflets. Transoesophageal echocardiography (TOE) showed aortic sclerosis without vegetation on the aortic or mitral leaflets. Abdominal computed tomography (CT) revealed a thickening of the abdominal infrarenal aorta wall taking the contrast, with a fusiform aneurysm located on the posterior wall (Figure 1). ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) demonstrated intense and diffuse hyperactivity of the thoraco-abdominal aorta, subclavian arteries, and internal and external carotids bilaterally (Figure

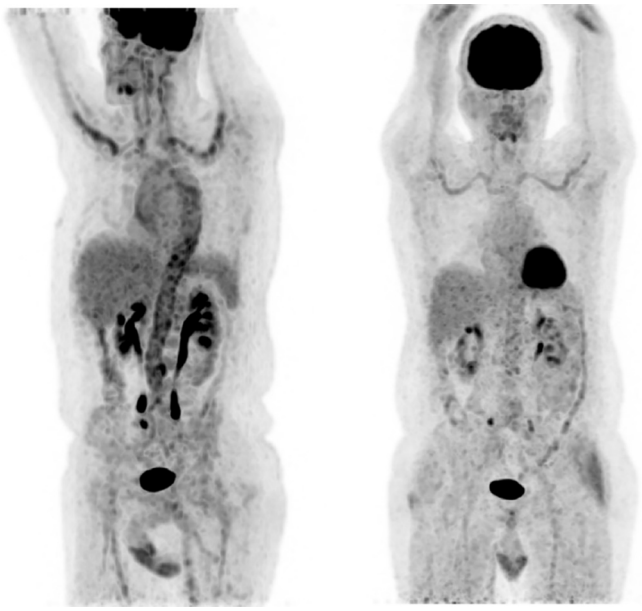

Figure 2. Sagittal sections of ^{18}F-FDG PET/CT centred on the abdominal aorta. Left: diffuse hyperactivity of the walls of the thoraco-abdominal aorta, subclavian and axillary arteries, and carotids. The aneurysm located on the posterior wall of the infrarenal aorta presents more intense hyperactivity. Right: follow-up after 4 months of antibiotics and corticosteroids, showing almost complete resolution of the aorta wall hyperactivity. Moderate hyperactivity of the subclavian arteries persists.

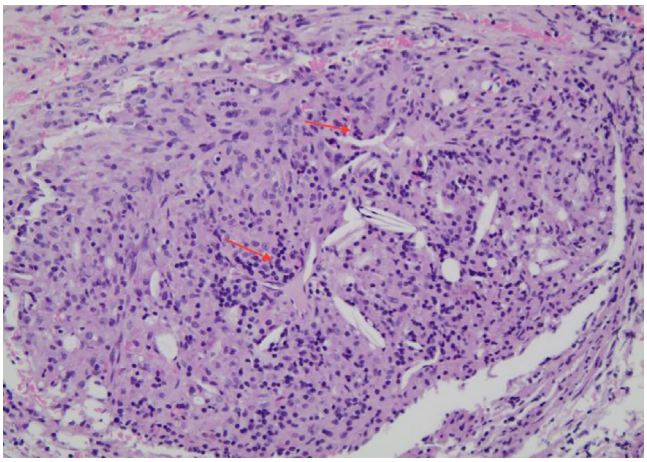

Figure 3. Focus (magnification ×20) on a granuloma with rare giant cells (arrows). The white central structures correspond to crystals of cholesterol.

Table 1
Antibody titres against *Coxiella burnetii* (indirect fluorescence technique)

Date	Phase I antigens			Phase II antigens		
	IgA	IgM	IgG	IgA	IgM	IgG
11/07/2016[a]	ND	512	4096	ND	<32	2048
04/08/2016	Aortic surgery					
10/08/2016[a]	ND	512	512	ND	<32	256
15/08/2016[b]	0	0	400	0	0	400
23/11/2016[a]	ND	<32	256	ND	<32	64
22/02/2017[a]	ND	<32	128	ND	<32	<64
26/05/2017[a]	ND	<32	128	ND	<32	<64

ND, not done.
[a] Done at the Institute of Tropical Medicine in Belgium.
[b] Done at the French National Referral Centre for Q Fever. The two laboratories used different assays.

2). The diagnosis of GCA was retained without performing a temporal artery biopsy. Prednisolone was started at 64 mg once a day.

Given the covered rupture of the pseudo-aneurysm, the aorta was replaced with an allograft 3 weeks later (August 4, 2016). An allograft was preferred to endovascular treatment using a stent graft because infectious aortitis could not be excluded. Histology of the surgical specimen revealed intense aortitis with a significant inflammatory infiltrate (mainly lymphocytes and plasmocytes), rare foci of giant cell granuloma without necrosis, calcifications, and footprints of cholesterol crystals (Figure 3). These features suggested aortitis due to atherosclerosis and a dissection of the aorta.

At the same time, a positive result for the *C. burnetii* serology was received, compatible with a persistent focalized infection (Table 1). PCR and culture were thus performed on peri-aortic tissue sampled during the surgery. PCR was positive for two genes (*IS1111* and *IS30a*) specific to *C. burnetii* and culture was positive 1 month later (Figure 4). PCR on blood was negative. Immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH), performed as reported previously (Melenotte et al., 2016), were negative. A combination of hydroxychloroquine 600 mg once a day and doxycycline 100 mg twice a day was added to the slowly tapered prednisolone upon receipt of the serology result. The antibiotic therapy was recommended by the French National Referral Centre for Q Fever for a duration of 24 months.

At 14 months of follow-up, the patient was doing well, except for mild photosensitivity reactions on the sun-exposed area due to doxycycline. A control PET scan 4 months after the beginning of antibiotic therapy showed almost complete disappearance of the aortic wall hyperactivity (Figure 2). The follow-up of antibodies showed a favourable progression (Table 1). Concentrations in the serum of 5–10 μg/ml for doxycycline and 1 ± 0.2 μg/ml for hydroxychloroquine are recommended (Eldin et al., 2017). Drug monitoring after 3 months of therapy showed levels of 8.95 μg/ml for doxycycline and 1.75 μg/ml for hydroxychloroquine. Thus hydroxychloroquine was reduced to 200 mg twice daily, and subsequent levels were within the recommended range.

3. Discussion

A new case of vascular infection due to *C. burnetii* involving the abdominal aorta is described, although the patient also fulfilled the criteria for GCA.

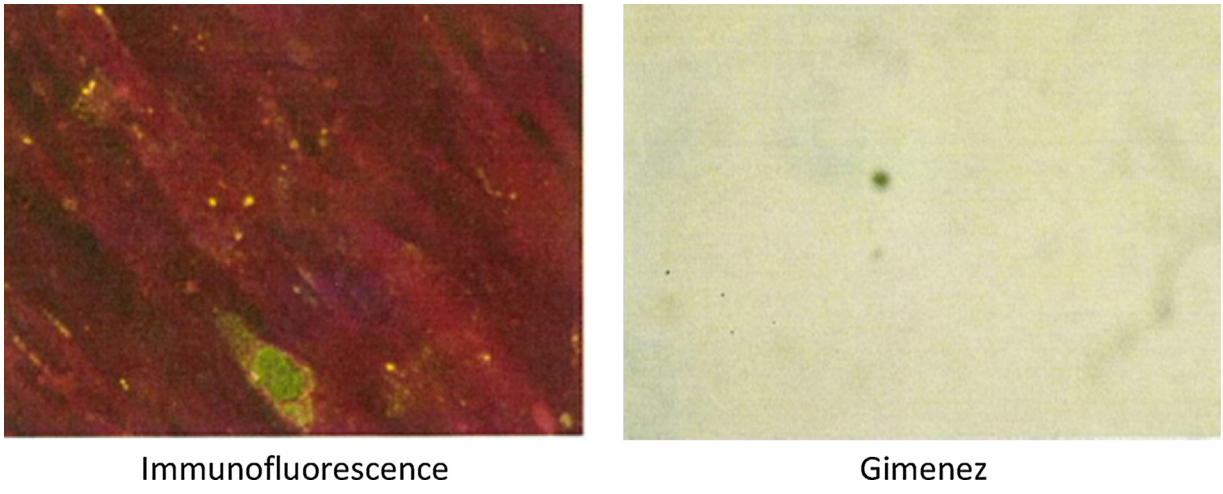

Figure 4. Immunofluorescence in cell culture medium, showing *Coxiella burnetii* antigen detection, as well as Gimenez staining.

At least 230 cases of *C. burnetii* vascular infection (aneurysms or vascular grafts) have been reported, mostly affecting the abdominal aorta (Botelho-Nevers et al., 2007; Edouard et al., 2013; Eldin et al., 2016; Wegdam-Blans et al., 2011), and similar to *C. burnetii* endocarditis, they were classically considered as chronic diseases. These infections are highly chronic. However, a diagnosis of chronic Q fever should not be retained on the sole basis of biological criteria (serology or molecular biology) without clinically evident infection. Hence, the vague term 'chronic Q fever' should be replaced by anatomically well-defined diseases (endocarditis, vascular or bone and joint infections) (Million and Raoult, 2015; Million and Raoult, 2017).

The elevated levels of antibodies against phase I antigens led to the suspicion of a cardiovascular infection, but such infections are also reported in patients with low titres of phase I IgG (Edouard et al., 2013). Notably, follow-up antibody detection (performed in two laboratories) (Table 1) showed concordant rapid and pronounced decreases in the levels of antibodies against phase I antigens after the surgery (August 4, 2016), as already observed in other cases (Eldin et al., 2016). A definite diagnosis of Q fever vascular infection could be retained here (positive culture and PCR of the aorta is sufficient for this purpose, but one major and three minor criteria were also found; A1B2C3) (Raoult, 2012). Negative IHC and FISH results do not exclude the diagnosis, because the sensitivities of these methods are not perfect. Endocarditis cannot be ruled out since valvular involvement can be as minimal as thickening or sclerosis without vegetation and the saccular aneurysm can be an embolic consequence of endocarditis, so the vascular infection could have been associated with a possible endocarditis (Raoult, 2012).

The diagnosis of GCA associated with Coxiella infection versus infectious aortitis only is the subject of discussion. Giant cells are rare and surround crystals of cholesterol. However, the case patient fulfilled four of the criteria of the American College of Rheumatology (ACR) classification of vasculitis (age >50 years, tenderness of the temporal arteries, ESR >50 mm/h, and granuloma with multinucleated giant cells) (Hunder et al., 1990). The hyperactivity of the entire aorta on ^{18}F-FDG PET/CT may be another argument for GCA, since it appears that no case of Coxiella infection affecting the whole aorta has been reported previously. Baziaka et al. described a case of global aortitis following acute Q fever, but they concluded that the patient had an inflammatory disease, which was treated with methylprednisolone and methotrexate, although the patient also received doxycycline and hydroxychloroquine for more than 1 year (Baziaka et al., 2014). Of note, the patient described by Baziaka et al. fulfilled the ACR criteria for GCA, although it was reported as a 'Takayasu-like' aortitis. Finally, the favourable clinical and biological outcomes in the case presented here, who was treated with prednisolone alone before surgery and antibiotics (CRP had normalized at the second hospital admission for surgery) are in favour of GCA.

Positive IgM anticardiolipin and anti β2 GP1 antibodies were found in the patient reported by Baziaka et al., but IgG anticardiolipin (other antiphospholipid tests were not performed) was normal in the patient case presented herein; however the patient of Baziaka et al. presented an acute Q fever with a heart valve vegetation, recently reported as a new clinical entity (Million et al., 2016).

Severe atherosclerosis (obvious on the abdominal CT) undeniably favoured Coxiella aortitis, which could have been in turn a trigger for GCA. The involvement of infectious agents in at least some cases of GCA is probable, and varicella zoster virus has recently been suspected as a causal agent (Nagel et al., 2013; Nagel and Gilden, 2014). Including the case of Baziaka et al., the association of GCA and Q fever appears to have been described only three times in the literature from 1994 to 2014 (Lefebvre et al., 2010; Odeh and Oliven, 1994; Baziaka et al., 2014). Fortuitous associations could be suspected, but a pathophysiological link between the two conditions is likely. Vascular *C. burnetii* infections are probably under-diagnosed, as could be the involvement of *C. burnetii* in GCA, and corticosteroid therapy can mask infectious aortitis, at least transiently. Clinicians should be aware of this agent when exploring aortitis and/or persistent fever in patients with risk factors for previous exposure (e.g., leisure, hunting).

PET/CT is useful to identify cardiac, vascular, and osteoarticular Q fever in patients with unexplained increases in *C. burnetii* antibodies (Eldin et al., 2016; Eldin et al., 2017; Million and Raoult, 2015).

The French National Referral Centre for Q Fever recommends testing surgical aortic specimens for Coxiella (PCR and culture), especially for non-degenerative diseases, and to screen for abdominal aneurysm in patients with acute Q fever older than 65 years or with a family history of aneurysm. A prophylactic 12-month treatment with hydroxychloroquine and doxycycline should be proposed for patients with acute Q fever and aortic aneurysm or prosthesis (Eldin et al., 2016; Million and Raoult, 2015). As for *C. burnetii* endocarditis, this strategy aims to decrease the occurrence of vascular *C. burnetii* infections, which are currently associated with a mortality rate of 18–25% (Eldin et al., 2016).

Overall, this report highlights the importance of *C. burnetii* vascular infections, which currently represent the most severe risk among non-pregnant adults, as mortality rates for endocarditis have dropped below 10% since the optimization of therapeutic protocols with doxycycline and hydroxychloroquine (Million et al., 2010). Future studies should further clarify the direct (infectious) or indirect (non-infectious auto-immune or inflammatory) mechanisms that make *C. burnetii* a potentially lethal pathogen for humans through vascular lesions, as previously demonstrated for endocarditis (Eldin et al., 2016).

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