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Case Report

Q Fever Endocarditis Mimicking Lymphoma and ANCA-Associated Vasculitis: Two Cases and a Literature

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Abstract: Q fever endocarditis may be accompanied by immunological abnormalities complicating the diagnosis. We report two cases of Q fever endocarditis mimicking lymphoma and ANCA-associated vasculitis illustrating the immune disorders that can be triggered by *Coxiella burnetii*.

Keywords: Q fever; *Coxiella burnetii*; lymphoma; ANCA-associated vasculitis; immunity; cryoglobulinemia; autoimmune hemolytic anemia

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1. Introduction

Q fever is a zoonosis caused by the obligate intracellular bacteria *Coxiella burnetii*.

Up to 60% of infected people are asymptomatic, but there is a wide spectrum of clinical manifestations associated with Q fever. Acute Q fever usually manifests as a flu-like illness, pneumonia, hepatitis or acute endocarditis. Q fever can also cause chronic endocarditis, vascular infection and osteomyelitis.

There is a close relationship between *Coxiella burnetii* infection and immune dysfunction, suspected for several years with the frequent association of Coxiella with autoantibodies such as anti-cardiolipid (47–81%) and anti-Ac smooth muscles (23–29%), which can make diagnosis even more difficult [1].

We report two cases of Q fever endocarditis mimicking lymphoma and ANCA-associated vasculitis illustrating the immune disorders than can be triggered by *Coxiella burnetii*.

2. Case 1: Q Fever Endocarditis Presenting as Lymphoma

A 67-year-old man was hospitalized in our department for a deterioration of his general condition with evening fever and night sweats for three months.

His medical history consisted of rhythmic and valvular heart disease with aortic and mitral bioprosthesis and a tricuspid plasty.

Two years after the last heart surgery and following an inguinal hernia repair, the diagnosis of endocarditis with negative blood culture was retained with the presence of a fever associated with an 18 mm vegetation on the mitral bioprosthesis on cardiac echography and TEP scan. The patient was treated with daptomycin and rifampicin for 6 weeks. The evolution was initially favorable with apyrexia and regression of the vegetation. Six months later, the patient had a relapse of fever associated with a reappearance of the biological inflammatory syndrome with a C reactive protein (CRP) at 24 mg/L.

The clinical examination showed a hepatomegaly of 20 cm, a splenomegaly of 19 cm without peripheral lymphadenopathy and the known systolic murmur.

The biological assessment revealed an autoimmune hemolytic anemia with a hemoglobin dosage at 8.6 g/dL, indosable haptoglobuline and a positive Coombs test for IgG (+++). Protein electrophoresis found polyclonal hypergammaglobulinemia at 32 g/L (N < 15 G/L) associated with a cryoglobulinemia type IIb at 226 mg/L without consumption of the complement. The rheumatoid factor (RF) was positive at 51 UI/mL (N < 20 UI/mL) and antibodies to smooth muscles (ASMA) at 1/80. Anti-nuclear antibodies and anti-cardiolipid antibodies were negative. Serologies for HIV, HBV, HCV, *rickettsia*, *Bartonella* and brucellosis were normal. Blood cultures remained sterile.

Immunophenotyping of circulating lymphocytes and osteomedullary biopsy did not find evidence for lymphoma. Despite the significant hypergammaglobulinemia, no monoclonality was found in the blood and urine samples. The trans-esophageal echocardiography did not show any vegetation or prothesis dysfunction so the TEP scan and heart scan were considered to be normal.

The *Coxiella burnetii* serology, confirmed by the French National Reference Center (NRC Marseille), was positive at 1/12,800 in phase 1 and 2 with IgG (N < 1/800), as well as the qualitative Polymerase Chain Reaction (PCR) in the blood [2].

The patient therefore fulfilled the Dutch criteria for chronic Q fever and the Raoult criteria for Q fever endocarditis [3].

Treatment with doxycycline 200 mg per day and hydroxychloroquine 600 mg per day was started for a scheduled duration of 24 months with a favorable evolution (Table 1).

Table 1. Evolution of patient 1 under treatment.

Months after Diagnosis	Fever	Serology		*Coxiella burnetii* PCR	Hemoglobin (g/dL)	Coombs Test	Cryoglobulinemia (mg/L)
		Phase 1 IgG	Phase 2 IgG				
M0	Presence	1/12,800		positive	8.6	IgG+++	226
M3		1/6400		negative	11.3	IgG++	13
M7	Absence	1/3200		NA	12.1	IgG+	25
M12		1/1600			13.1		27

A monthly dosage of hydroxychloroquine (target 0.8–1.2 µg/mL) and doxycycline (target 5–10 µg/mL) was administered for monitoring.

3. Case 2: Q Fever Endocarditis Mimicking ANCA-Associated Vasculitis

A 42-year-old man was referred to our unit department because of chronic fever associated with a vascular purpura and polyarthralgia.

Two years prior, the patient presented an endocarditis without bacterial identification on his mechanical valve installed 20 years prior. He was treated by broad spectrum antibiotic therapy with good evolution.

The patient developed intermittent fever, followed by polyarthralgia and purpura vascular 2 months after.

The physical examination highlighted fever at 39 °C, petechial purpura rash of the legs and polyarthralgia without arthritis. Blood tests revealed elevation of the inflammatory markers with a CRP at 110 mg/L, normocytic anemia at 8.3 g/dL without augmentation of reticulocyte and thrombopenia at 98,000 G/L. Protein electrophoresis found polyclonal hypergammaglobulinemia at 26 G/L (N < 15 G/L) concomitant with a positive rheumatoid factor at 83 U/L (N < 20 UI/mL). Blood cultures remained sterile without prior antibiotics. Proteinuria, renal and liver function were normal. Cryoglobulinemia was not present. Immunophenotyping of circulating lymphocytes and osteomedullary biopsy were normal.

Two trans-thoracic echographs (TTE) were normal. The CT of the chest, abdomen and pelvis and PET-CT with cardiac analysis found only a splenomegaly at 15 cm.

Finally, the ANCA-PR3 dosed with ELISA returned positive at the rate of 157 CU (N < 20) as well as the serology of Q fever in IgG (phase 1: 1/8192, phase 2:1/8192 (N < 1/800)).

At this point, two diagnostics were discussed: Q fever endocarditis or ANCA-associated vasculitis with articular and skin involvement.

Another TTE was performed, one month after the previous one, showing a vegetation of 10 mm of the aortic valve with prosthetic disinsertion, confirmed by trans-esophageal echocardiography. Two days after starting antibiotic therapy, the patient developed severe abdominal pain revealing a splenic infarct.

The therapy consisted of an urgent valvular replacement associated with a bi-antibiotic therapy of doxycycline (200 mg per day) and hydroxychloroquine (600 mg per day) for 24 months. The evolution was favorable (Table 2).

Table 2. Evolution of patient 2 under treatment.

Months after Diagnosis	Physical Examination			Serology		CRP (mg/L)
				Phase 1 IgG	Phase 2 IgG	
M0	fever	vascular purpura	arthralgia	1/8192		110
M1	absence					<5
M3				1/16,384		
M6				1/4096		
M12				1/2048		

Although *Coxiella burnetii* PCR was negative on the infected valve, the patient fulfilled the Dutch and Raoult criteria for proven Q fever endocarditis.

4. Discussion

Our cases illustrate the main difficulties in diagnosing Q fever endocarditis.

First of all, *Coxiella burnetii* does not grow in a routine blood culture and requires specific research by serology. Out of 819 patients with negative blood culture endocarditis, *C. burnetii* was the main identified etiological agent (57.3%) [4]. Moreover, valvular vegetations are difficult to detect in TTE making it difficult to confirm the diagnosis of endocarditis. In the largest cohort of 104 patients of Q fever endocarditis, vegetations are detected in only 28% of the cases. The most frequent echocardiographic feature at diagnosis is the discovery or worsening of valvular insufficiency in 75% of the patients [5]. No evidence of endocarditis was found in our first patient, and for the second case, it was the third echography that showed vegetation, whereas the previous TTE and the PET-CT were considered normal. It seems important to repeat the TTE when there is a high suspicion of Q fever endocarditis.

Biological abnormalities can delay the diagnosis, particularly the presence of immunological disorders. Positive tests for ANCA, especially C-ANCA and P-ANCA, were reported in patients with subacute bacterial endocarditis. Among 109 patients with infective endocarditis, Mahr et al. found that C-ANCA and/or pANCA by indirect immunofluorescence assay (IF) were detected in 20 patients (18%) and PR3-ANCAs or MPO-ANCAs (by ELISA) in 8 patients (7%) [6]. During Q fever infection, the presence of ANCA during Q fever infection was estimated at 12% [7] in immunofluorescence but dosage with ELISA was not performed in this study. Positivity of MPO and PR3 dosage in Q fever was reported in at least two other observations [8,9], suggesting a nonspecific immune activation. Interestingly, Bartonella infection, the second most common germ in culture-negative endocarditis, seems to have a higher rate of ANCA positivity with 40% PR3-ANCA antibodies [10]. However, this characteristic seems specific to *B.quintana* lipopolysaccharide apoptotic behavior [11]. Clinicians should be aware of the false positivity of ANCA dosage in Q fever infection.

Cryoglobulinemia was reported in Q fever infection, with at least six cases published. Immunosuppressive therapy was used in several cases with clinical worsening leading to the diagnosis of Q fever [12]. Autoimmune hemolytic anemia is less reported, with three cases and only one in English [13]. Our case is the first one, to our knowledge, presenting these two rare immunological complications. This supports the dysfunction of B-cells, and complicates the differential diagnosis of lymphoma and autoimmune disease. Other

unusual presentations of Q fever have been noticed such as Crohn's disease, Goodpasture's syndrome, adult-onset Still's disease, polyarteritis nodosa and giant-cell arteritis [14].

Our two patients have similarities. They both are middle-aged men; have undergone valvular replacement, which fits well with the epidemiology of chronic endocarditis; and with a sex ratio at three and a prevalence of predisposing heat disease at 95% [5]. They also have a history of endocarditis with sterile blood culture. We can reasonably presume that Q fever was already involve. This observation reinforces the need to search for *Coxiella burnetii* in front of endocarditis with negative blood culture.

Q fever infection is transmitted to humans mainly by inhalation of infected particles from herds of goats or sheep. In our patients, no animal exposure was identified, but the second lived in a rural area.

With multiple presentations of Q fever, clinicians should not hesitate to carry out a serology when faced with an atypical situation evoking hemopathy, vasculitis or auto-immune disorders, especially in a patient with predisposing valvular heart disease.

5. Conclusions

Q fever endocarditis must be considered in the case of chronic fever in a patient with predisposing valvular heart disease, even in manifestations evoking vasculitis or auto-immune disorders.

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