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Brief Report

Culture negative endocarditis combined with glomerulonephritis caused by *Bartonella* species in two immunocompetent adults

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Abstract

Two cases of culture negative endocarditis are presented. In both, *Bartonella* species could be identified as the causative agent and in one of them *Bartonella henselae* was very likely. Both cases were accompanied by glomerulonephritis, in one case proven by a kidney biopsy. A nephrotic syndrome may be the first presentation of an endocarditis caused by *Bartonella* species.

Keywords: Nephrotic syndrome; Endocapillary proliferative glomerulonephritis; *Bartonella henselae*

Introduction

The nephrotic syndrome is characterised by the urinary loss of plasma proteins due to an increase in permeability of the glomerular membrane. The main clinical features are proteinuria, hypoproteinaemia and edema. Among the causes of the nephrotic syndrome are both renal and extrarenal pathology. One of the extrarenal causes is endocarditis. The etiology of the glomerular changes in endocarditis is probably the subepithelial deposition of immunecomplexes with complement factors along the basal membrane of the glomerulus. These depositions lead to a diffuse or focal glomerulonephritis.

The most important bacterial agents causing endocarditis are streptococci, enterococci and staphylococci, in the latter group especially *S. aureus*. Unfortunately, in 5–10% of the patients blood cultures remain negative and serological tests are necessary to establish the correct diagnosis. Within this group of culture negative endocarditis (CNE), *Bartonella henselae* is nowadays a frequently found pathogen [1–7]. The combination of endocarditis and postinfectious glomerulonephritis caused by *Bartonella* species has not been documented before.

Case histories

Patient A

A 53-year-old male, was admitted to our hospital because of proteinuria found by the general practitioner in the workup for long-term fatigue. Only 4 months earlier he had visited Israel in perfect health. The fatigue existed for 2 months and was accom-

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panied by perspiration and headache. He also experienced dyspnoea in exercise and in supine position, edema of the legs and markedly reduced appetite. Furthermore he had a dry cough and palpitations.

There was no history of use or abuse of any substance and no family-history of cardiovascular disease. He could not remember being scratched or bitten by house pets.

The physical examination showed a pale, not acutely ill male. Body temperature was 37.8°C. The blood pressure was 160/90 mmHg, the central venous pressure was elevated (R + 1). There were no palpable lymphomas in the head and neck region or elsewhere. Auscultation of the heart revealed a systolic murmur grade 2/6 and a diastolic murmur over the aortic area and also a grade 3/6 systolic murmur consistent with mitral valve insufficiency. Over the lungs, crackles were heard at the base on both sides and there was a dull percussion at the left dorsobasal level. The liver appeared to be normal in size, the spleen could be palpated two fingers wide under the left costal border. The extremities were edematous with normal pulsations of the peripheral arteries. The rectal examination revealed no abnormalities.

Laboratory tests revealed anaemia and an elevated ESR and CRP with a normal amount of leucocytes and an elevated level of urea nitrogen and creatinine. The level of the serum albumen was decreased and there was a proteinuria of 8.25 g/l which turned out to be selective (selectivity index = 0.07) as usually only seen in minimal lesions glomerulonephritis (Table 1).

Table 1
Laboratory tests results

	Patient A	Patient B
ESR (mm)	94	80
Hb (mmol/l)	6.0	8.0
Ht (l/l)	0.28	0.38
Erythrocytes (10E12/l)	3.50	4.55
MCV (fl)	79.4	83.3
MCH (fmol)	1.71	1.76
MCHC (mmol/l)	21.6	21.1
Leuco (10E9/l)	5.3	13.4
Thromb (10E9/l)	176	470
Na (mmol/l)	136	136
K (mmol/l)	5.2	4.6
Urea (mmol/l)	28.2	4.9
Creat. (μmol/l)	181	97
Albumen (g/l)	25.9	28
Tot. protein (g/l)	62.9	79
CRP (mg/l)	32	78
ANCA	Neg	Neg
ANA	Neg	Neg
HLA-B27		Neg
Anti-TBM		Neg
Anti-GBM		Neg
C1q (μg/ml; $N < 1.5$)	5.7	2.9

The ECG did not show specific abnormalities, and the Galliumscan and the echographic examination of the abdomen were normal.

Taking together the results of the history, the physical examination and the first laboratory tests, the most likely hypothesis was that the patient suffered from endocarditis. An echocardiographic examination was performed which showed a slightly dilated left ventricle with normal contractions and a clearly pathologically deformed aortic valve. The valve showed a systolic gradient of 85 mmHg and mild regurgitation. The mitral valve also showed moderate regurgitation. Further examination by means of transoesophageal echocardiography showed two round echodense lesions on the aortic valve (Fig. 1).

The findings of the cardiological tests strongly supported the working hypothesis of endocarditis. The patient was treated with enalapril and furosemide because of the regurgitation. No antibiotics were given at this stage. In search for the origin of the endocarditis, extensive examinations and tests were performed (Table 2). The multiple arterial and venous blood cultures remained negative. Because of the nephrotic syndrome the patient underwent a kidney biopsy, which revealed a diffuse endocapillary proliferative glomerulonephritis with focal segmental glomerulosclerosis and necrosis corresponding to postinfectious glomerulonephritis as seen in endocarditis (Fig. 2).

With the diagnosis of CNE and persistent elevated body temperature, antibiotic therapy was started with ceftriaxone 2 g once daily i.v. With this regimen the temperature remained elevated. After 14 days of treatment the serological tests revealed a high titre of antibodies against *Bartonella* species (IFA technique) and netilmicin (5 mg/kg) was added to the regimen.

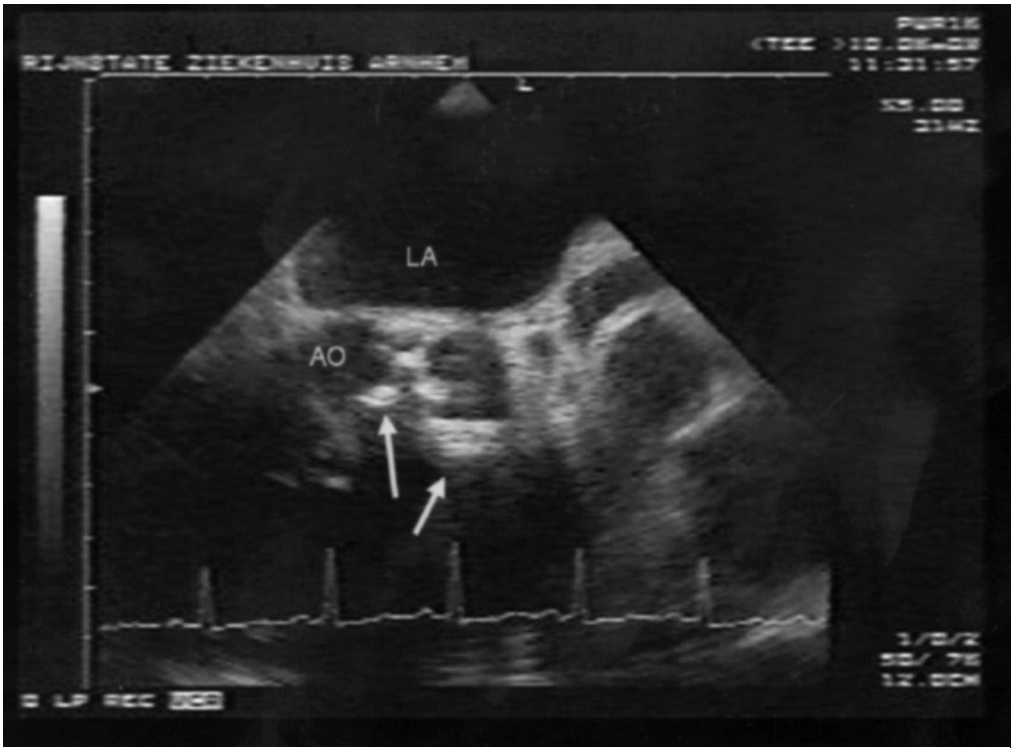

Fig. 1. Transoesophageal echocardiogram showing two round echodense lesions on the aortic valve of patient A.

Table 2
Microbiological and serological examination

	Patient A	Patient B
Para-influenza 1,2,3	IgM neg	
Influenza	IgM neg	
Mycoplasma pneumoniae	IgM and IgA neg (Elisa)	
Listeria type 1 and 4b	$<1{:}4$	
Listeria type 1H, 1O 4bh, 4bO	Negative	
Yersina enterocolitica	Negative	
HBsAg, anti-HBs, anti-HBc, anti-HC	Negative	
Bartonella antibodies	IgG $1 \geq 256$	IgG $1 > 850$ (1:3200)
	IgM $1 \geq 128$ (Ifa)	IgM $1 < 200$ (Elisa)
Chlamydia pneumoniae		IgG positive
Coxiella burnetti		IgG and IgM negative
Brucella		Negative
Epstein–Barr		Negative
Hanta virus		Negative
Toxoplasmose		Negative
anti-HIV	Negative	
Bloodcultures (venous and arterial)	All 23 negative	All seven negative

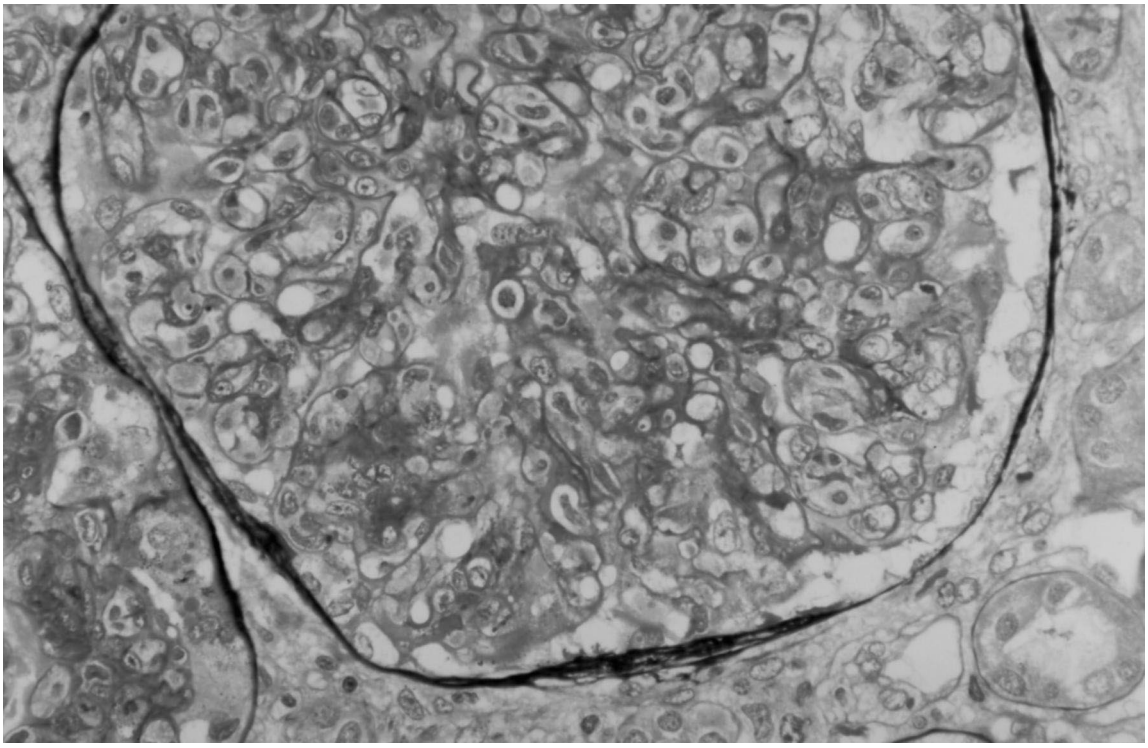

Fig. 2. Kidney biopsy showing diffuse endocapillary proliferative glomerulonephritis with focal segmental glomerulosclerosis and necrosis corresponding to postinfectious glomerulonephritis as seen in endocarditis.

Still there was no definitive normalization of the body temperature and the patient developed a leucopenia. This was the reason to exchange the netilmicin for erythromycin. This combination also did not result in clinical improvement and it was decided to change the treatment to a combination of ceftazidim (1 g i.v., three times daily) and ofloxacine (200 mg i.v., twice daily).

As there was only minor improvement in the clinical situation and given the results of the trans-oesophageal examination, the patient was prepared for cardiac surgery. Heart catheterisation revealed a grade 3/4 aortic regurgitation, a non dilated left ventricle and no coronary sclerosis. The ascending aorta was found to be dilated up to the level of the a. anonyma. The maximal diameter appeared to be 5 cm on CT.

Cardiosurgery was performed on the 81st day after admission. An aortic valve replacement was performed (St Jude mechanical prosthesis) combined with an aortaplasty (St Antonius Hospital, Nieuwegein). The excised native aortic valve clearly revealed an endocarditis of a bicuspid valve. The microbiological tests on the native valve were inconclusive. The PCR on *B. henselae* was not positive due to an inhibiting factor (oral statement Dr M. Tersmette, St Antonius Hospital, Nieuwegein). Pathological examination of the aorta revealed slight fibrosis of the intima. Post-operative treatment consisted of Doxycyclin 200 mg twice daily for 6 weeks. During the follow up the urine analysis still showed proteinuria and the serum creatinine level decreased to 130 μmol/l. The antibody titre against *B. henselae* returned to normal.

Conclusion

Culture-negative endocarditis of the bicuspid aortic valve combined with dilatation of the ascending aorta and post infectious glomerulonephritis caused by *Bartonella* species.

Patient B

A 31-year-old male presented in May 1996 with fatigue, headache, fever with chills and uveitis anterior in both eyes. The symptoms had started 12 days before admission. During this period he had unsuccessfully been treated with ibuprofen and amoxicillin by his general practitioner. The medical history revealed no problems and gave no clues to the diagnosis. His daily job as an electrician frequently brought him in contact with soil and mud. Incidentally there were contacts with cats and dogs.

Physical examination was essentially negative, apart from red eyes and a body temperature of 39.1°C. Blood pressure was 130/65 mmHg, heart sounds were normal without the presence of murmurs.

Laboratory investigations showed an ESR of 80 mm and a CRP of 78 mg/l, Hb 8.0 mmol/l, creatinine 95 μmol/l, serum albumin 28.8 g/l and a leucocytosis of 13.5×10^9/l. The urine contained 1.8 g/l of protein and the sediment showed granular and cellular casts with erythrocytes. All seven bloodcultures and a urine culture taken over a period of 21 days were negative. The results of the laboratory investigations are shown in Tables 1 and 2.

Because of the long duration of the febris intermittens (>3 weeks), a transthoracic echocardiographic examination was performed showing large (ca. 8 mm) vegetations on the left coronary cusp of the aortic valve, which was confirmed with transesophageal echocardiography (Fig. 3). The diagnosis of CNE was now finally made and i.v. treatment with a first choice of penicillin (12×10E6 U/day) combined with netilmicin (5 mg/kg per day) was started.

The netilmicin was stopped after 2 weeks of treatment to avoid toxic effects. The penicillin was replaced by ceftriaxone i.v. (2 g/day) after 3 weeks because of a renewed rise in temperature and ESR. The uveitis, in the mean time, had healed almost completely while the urine abnormalities resolved afterwards. After a total of 6 weeks antibiotic treatment the temperature normalised and the patient was discharged. Two months later the ESR had

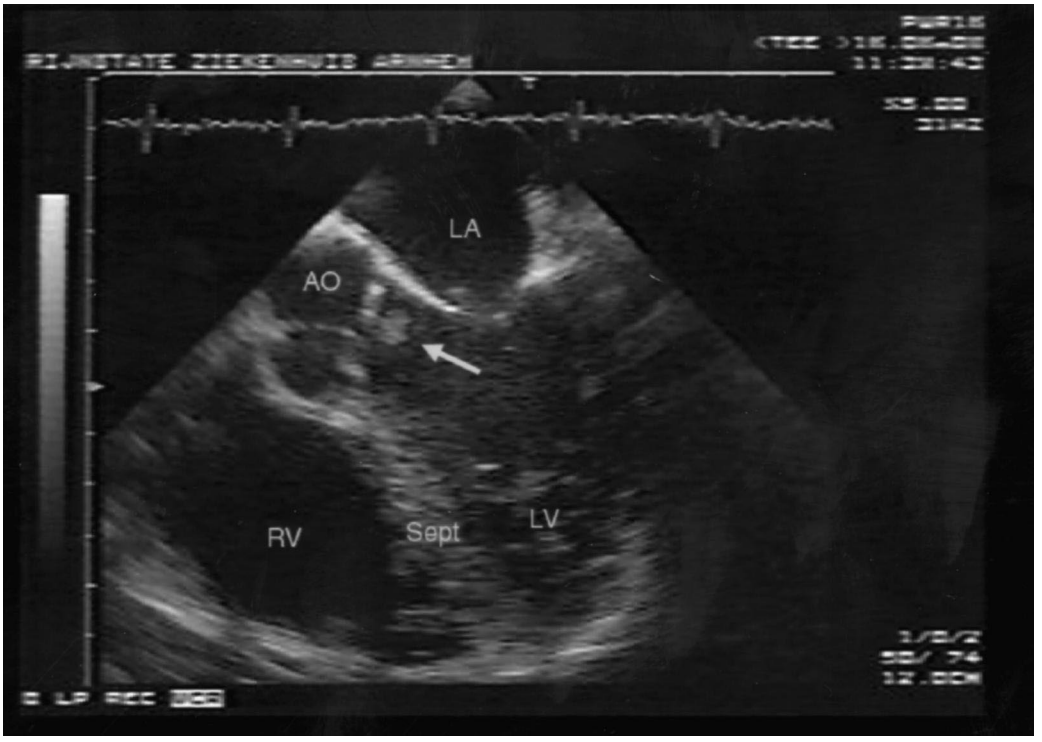

Fig. 3. Transesophageal echocardiogram showing large (ca. 8 mm) vegetations on the left coronary cusp of the aortic valve of patient B.

decreased to 10 mm and the CRP to 6 mg/l. The proteinuria disappeared and echocardiographically the aortic valve had normalised. After another 4 months, we checked for antibodies against *Bartonella* and found a very high titre in the IgG fraction without positive titre in the IgM fraction (Elisa technique).

Discussion

Both patients presented here show that endocarditis caused by *Bartonella* species can be accompanied by glomerulonephritis, or even present itself. To our knowledge this has not been reported before.

The diagnosis of a *Bartonella* infection depends largely on the serology. The sensitivity of serological tests in cat-scratch disease has proven to be low: indirect fluorescence assay IgG 40%, IgM 50%, enzyme-linked immunoassay IgG 10%, IgM 71% (specificity for all: $>95\%$). PCR showed the highest, but still suboptimal sensitivity: IgM 86%, requiring clinical material [8].

There have also been reports on serological cross reactions between *Bartonella* and *Chlamydia* species. It has been shown that patients with a PCR-proven *Bartonella quintana* endocarditis also had high levels of cross-reacting antibodies to *Chlamydia pneumoniae* and *C. psittaci*. This cross-reaction could be eliminated by absorbing the serum samples with *B. quintana* antigen [9]. Others have shown that there is no cross-reaction between *B. bacilliformis* and *B. henselae*, when using a sonicated diagnostic immunoblot, making it hard to interpret the meaning of the above mentioned cross-reactions for *B. henselae* infections [10].

Furthermore, an acute Epstein–Barr infection can substantially reduce the specificity of *B. henselae*-specific IgM tests, so a significant IgG titre to *B. henselae* seems to be required to confirm the diagnosis [11].

With all this in mind it is clear that we do not have totally proven that our patients suffered from *B. henselae* endocarditis.

In the case of patient A, the outcome of the IFA technique during the acute episode proved *Bartonella* infection but could not identify the subtype.

In patient B, using the Elisa technique based on the use of *B. henselae*-antigen, the very high titre of IgG antibodies (1:3200) makes it quite likely that in this case, *B. henselae* was the malefactor, especially because this titre was found several months after the acute episode. The positive titres against *C. pneumoniae* might be due to a cross-reaction. A primary endocarditis caused by *Chlamydia* seems very unlikely. The uveitis anterior in patient B may be caused by *Bartonella* infection but this remains speculative.

Reviewing these cases also raises some other questions. The first question is which antibiotic regimen has to be chosen. Our patients were finally treated with a third generation cephalosporin, in patient A combined with i.v. ofloxacin. There is no ‘communis opinio’ in the literature. Optimal therapy is unknown. Erythromycin, azithromycin and doxycycline have been used with variable success [6]. Treatment is largely empirical. In a recent review article on *Bartonella* species, Maurin et al. stated that only aminoglycosides show bactericidal activity against intracellular *Bartonella* species in vitro and therefore are recommended as the antibiotics of first choice [12].

The second question is how long one has to wait for clinical improvement before deciding that the antibiotic drugs chosen are not effective. Suggestions from the literature vary from 4 weeks to 4 months.

The use of corticosteroids in glomerulonephritis also is not without discussion. It has been shown to be effective in selected cases in which the renal function deteriorated in spite of adequate antimicrobial therapy [13].

Conclusion

Two cases of culture negative endocarditis are presented. In both, *Bartonella* species could be identified as the causative agent and in one of them *B. henselae* was very likely. Both cases were accompanied by glomerulonephritis, in one case proven by a kidney biopsy.

A nephrotic syndrome may be the first presentation of an endocarditis caused by *Bartonella* species.

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