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BRIEF REPORT

"Let the Cat Out of the Heart": Clinical Characteristics of Patients Presenting With Blood Culture-Negative Endocarditis Due to *Bartonella* Species

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Patients with blood culture-negative endocarditis due to *Bartonella* infection frequently presented with fever, cytopenias, kidney failure, and positive PR3-ANCA. *Bartonella* IgG titers were variable. Patients commonly underwent surgery with overall low mortality.

Keywords. bartonellosis; cat-scratch disease; infective endocarditis; prosthetic valve endocarditis; renal vasculitis.

Bartonella species (spp) are fastidious, Gram-negative, facultative intracellular pathogens with a unique tropism for erythrocytes and endothelium [1]. There are several *Bartonella* spp that can cause a wide spectrum of syndromes in immunocompetent and immunocompromised individuals, with the most important human pathogens being *Bartonella bacilliformis* (etiology of Carrion's disease), *Bartonella henselae* (etiology of cat-scratch disease), and *Bartonella quintana* (etiology of trench fever) [2]. *Bartonella* spp are also an important and underrecognized cause of blood culture-negative infective endocarditis (BCNE) in humans [3–5]. Cats are the reservoir for different *Bartonella* species that can cause BCNE, and they are considered the main reservoir for *B henselae*, which is transmitted to humans from a cat scratch or through the cat flea, *Ctenocephalides* [2]. In this study, we aim to describe the clinical characteristics of patients with BCNE due to *Bartonella* spp at our institution.

METHODS

This was a retrospective study of adult patients with *Bartonella* endocarditis at Mayo Clinic in Rochester, Minnesota from November 1, 2005 to June 30, 2021. All patients had the diagnosis of "possible" or "definitive" infective endocarditis based on the modified Duke criteria [6]. The microbiologic criteria included positive *Bartonella* serology (*B henselae* or *B quintana* with immunoglobulin G [IgG] antibody titer ≥1:128) and/or molecular testing (positive *Bartonella*-specific polymerase chain reaction [PCR] or 16S rRNA broad-range PCR) from blood and/or valvular tissue and/or positive Warthin-Starry stain in pathology. All patients had negative blood cultures. Collected data included demographic characteristics, risk factors, clinical presentation, diagnosis, and management. After the diagnosis, 1-year follow up was performed in all patients who had available medical records.

Patient Consent Statement

The Mayo Clinic Institutional Review Board approved the study protocol. Patient consent was waived, but all included patients authorized the use of their medical records for research.

RESULTS

Presentation

Sixteen patients were diagnosed with *Bartonella* endocarditis during the study period (Table 1). Most patients had prior prosthetic cardiac valves (62.5%) and exposure to cats (62.5%), but other risk factors such as a history of autoimmune disorder (43.8%), chronic kidney disease (37.8%), and concurrent use of immunosuppression (37.8%) were also observed. The median duration of illness was 24 weeks (IQR, 12–33), and the majority presented with fever (87.6%), malaise (81.3%), and weight loss (56.3). All except 1 of the patients had anemia (93.8%), and other cytopenias were also frequent. Nine (56.3%) patients presented with new or worsening renal failure on admission, and 6 of them had positive proteinase 3 antineutrophil cytoplasmic antibodies (PR3-ANCA). Three patients were misdiagnosed with renal vasculitis, and their renal function improved with antimicrobial therapy. Four (25%) patients presented embolic phenomena (3 patients with emboli to the brain and 1 to the spleen).

Diagnosis

Transesophageal echocardiography showed valvular vegetations or masses in 13 (81.3%) patients, with frequent involvement of the aortic (56.3%) and mitral valve (31.3%). Perivalvular extension or aortic root abscesses were seen in 4 (25%) patients.

Serology titers for *B henselae* and *B quintana* were variable, with IgG titers as high as 1:262 144 for *B henselae* or as low as IgG 1:128 in a patient with a recent diagnosis of human

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Table 1. Clinical Characteristics of Patients Diagnosed With *Bartonella* Endocarditis (N = 16)

Clinical Characteristics	N = 16 (%)
Gender	
• Male sex	12 (75)
• Female sex	4 (25)
Age in years, median (IQR)	57 (50–66)
Comorbidities/Risk Factors	
• Prosthetic cardiac valve	10 (62.5)
• Cat exposure	10 (62.5)
• Autoimmune disorder	7 (43.8)
• Chronic kidney disease (>3 months)	6 (37.8)
• Use of immunosuppression (>1 months)	6 (37.8)
• Diabetes mellitus	4 (25)
• HIV	1 (6.3)
• Alcohol abuse	1 (6.3)
Time of illness, median, weeks (IQR)	24 (12–33)
Clinical Presentation	
• Fever	14 (87.6)
• Malaise	13 (81.3)
• Weight loss	9 (56.3)
• Volume overload	4 (25)
• Rash	4 (25)
Laboratory Testing	
• Anemia	15 (93.8)
• Other cytopenias	9 (56.3)
• Renal failure	9 (56.3)
• Abnormal liver enzymes	6 (37.5)
Immunology	
• PR3-ANCA positive/tested	6/9 (66.7)
• MPO-ANCA positive/tested	1/9 (11.1)
• Low complement positive/tested	6/9 (66.7)
Imaging	
• Splenomegaly	5 (31.3)
• Embolic phenomena	4 (25)
• Hepatosplenomegaly	2 (12.5)
Echocardiogram	
• Vegetation/mass	13 (81.3)
• Valvular dysfunction	10 (62.5)
• Perivalvular/root abscess	4 (25)
Valvular Involvement	
• Aortic	9 (56.3)
• Mitral	5 (31.3)
• Pulmonary	2 (12.5)
• Tricuspid	1 (6.3)
Bartonella spp Serology[a]	
• IgG ≥128	16 (100)
• IgG ≥800	12 (75)
Bartonella spp Molecular Testing Positive[b]	
• Blood positive/tested	2/14 (14.3)
• Valve positive/tested	7/10 (70)
C burnetii testing positive/tested[c]	8/14 (57.1)
Duration of treatment, median, weeks (IQR)	7 (6–14)
Antibiotics	
• Doxycycline	15 (93.8)
• Gentamicin	9 (56.3)
• Rifampin	8 (50)
• Ceftriaxone	6 (37.5)
Time between diagnosis and surgical management, median, days (IQR)	26 (4–98)
Surgical Management	10 (62.5)
• Valve replaced/prosthetic valve	6/10 (60)
• Valve replaced/native valve	3/6 (50)
• Valve repair/native valve	1/6 (16.7)
Outcome[d]	
Combined surgical and medical (6/15)	
• Improvement/resolution	5 (83.3)
• Relapse/persistent disease	0
• Death	1 (16.7)
Medical Only (9/15)	
• Improvement/resolution	4 (44.4)
• Relapse/persistent disease	4 (44.4)
• Death	1 (11.2)

Abbreviations: ANCA, antineutrophil cytoplasmic antibodies; HIV, human immunodeficiency virus; IgG, immunoglobulin G; IQR, interquartile range; MPO, myeloperoxidase; PR3, proteinase antibody 3.

[a]Serology using indirect immunofluorescence assay.

[b]Molecular testing using real-time polymerase chain reaction (PCR) for *Bartonella* species deoxyribonucleic acid and PCR of a highly variable fragment of the 16S ribosomal ribonucleic acid (rRNA) gene. Tests were developed and interpreted by Laboratory Medicine and Pathology at Mayo Clinic.

[c]Serology using indirect immunofluorescence assay and molecular testing using PCR for *Coxiella burnetii*. Tests developed and/or interpreted by Laboratory Medicine and Pathology at Mayo Clinic (Rochester, Minnesota).

[d]Outcomes related to initial management in 15 patients who had follow-up information for 1-year postdiagnosis of *Bartonella* endocarditis.

immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS). Eight patients (50%) had reactive *Coxiella burnetii* serology. Molecular testing from blood and/or cardiac valve was performed in all patients. *Bartonella* PCR in blood was positive in 2 (14.3%) of the 14 patients who were tested, whereas it resulted positive in 7 (70%) of the 10 patients who had molecular testing on the explanted cardiac valve and/or tissue. A pathology report was available for 9 patients with explanted or repaired valves, and all of them reported healed or healing endocarditis. The Warthin-Starry stain was used in 3 explanted cardiac valves and only 1 tested positive.

Treatment

Doxycycline was the most commonly used antibiotic (93.8%), followed by gentamicin (56.3%) and rifampin (56.3%). Patients received different combinations of antibiotics, but the combination of doxycycline with gentamicin was the most frequent (Table 2). Of the 9 patients who received gentamicin for at least 2 weeks, 7 had a favorable outcome, but 2 patients, who received only medical treatment, had relapsing disease.

Ten patients (62.5%) required surgical management, with 6 patients undergoing surgery during the initial admission, and 4 patients were rehospitalized later for valvular replacement due to clinical deterioration while receiving medical therapy only. The average time between diagnoses and surgery was 46 days (0–180). Of the 10 patients who had prosthetic valve

Table 2. Case description of patients diagnosed with blood culture-negative endocarditis due to *Bartonella* species (N=16)

Patients	Age, Gender	Risk factors/ Comorbidities	Time of Illness (weeks)	Clinical Presentation	Laboratory/Imaging	Immunology Testing/ Renal Biopsy	*Bartonella* Serology/ *Coxiella burnetii* Testing	*Bartonella* PCR Testing	Echocardiogram Findings/ Pathology	Management	Outcome
Patient 1	57, male	Mitral and aortic prosthetic mechanical valves due to rheumatic heart disease, diabetes	8	Fever, malaise, dyspnea, purpuric rash in lower extremities, volume overload	Anemia, leukopenia, renal failure, hematuria, abnormal liver enzymes, splenomegaly	Low complement, positive RF, negative ANCA, anti-MPO, and anti-PR3 Unable to do a renal biopsy due to active anticoagulation	*Bartonella henselae* IgG 1:256, IgM <1:20 *Bartonella quintana* IgG 1:128, IgM <1:20 *Coxiella burnetii* PCR negative	*Bartonella* PCR negative in blood and valve	Vegetation on the atrial side of the mitral valve with mod-severe dysfunction Pathology: active endocarditis with bacilli in clusters (sample collected during readmission)	8 weeks of ceftriaxone and doxycycline, 2 weeks of rifampin	Initial improvement of symptoms, renal failure, and decline of *Bartonella* IgG titers; no evidence of vegetations in repeat echocardiogram Readmitted later due to valvular dysfunction and heart failure exacerbation, underwent mitral valve replacement with resolution of symptoms
Patient 2	85, male	CKD, recent use of PDN and AZA for 3 months due to presumed GPA, cat exposure	22	Fever, malaise, chills, dyspnea, purpuric rash in lower extremities	Anemia, acute on chronic renal failure, hematuria, abnormal liver enzymes	Low complement, positive ANCA, and anti-PR3, negative anti-MPO Renal biopsy: focal sclerosing pauci-immune GN (compatible with GPA)	*B. henselae* IgG 1:4096, IgM <1:20 *B. quintana* IgG 1:2048, IgM <1:20 *C. burnetii* was not tested	*Bartonella* PCR negative in blood	Vegetation in the right atrium attached to the tricuspid leaflet	6 weeks of doxycycline and rifampin Continued treatment for GPA with AZA	Resolution/ improvement of symptoms, no evidence of vegetations in repeat echocardiogram
Patient 3	33, male	Prosthetic aortic valve and root replacement due to bicuspid aortic valve	6	Fever, malaise, night sweats, chills, fatigue, volume overload	Anemia	Complement and ANCA not tested	*B. henselae* IgG 1:128, IgM <1:20 *B. quintana* IgG 1:256, IgM <1:20 *C. burnetii* serology negative	*Bartonella* PCR negative in blood and valve	Vegetation in the aortic valve with moderate to severe dysfunction with paravalvular and root abscess Pathology: fibrinous tissue with active infection (negative Warthin-Starry)	6 weeks of rifampin and levofloxacin, 2 weeks of gentamicin; aortic valve and root replacement	Resolution/ improvement of symptoms and *Bartonella* titers
Patient 4	59, male	Bicuspid aortic valve, cat exposure	8	Fever, malaise, weight loss, confusion, small purpuric lesions in the left hand	Anemia, thrombocytopenia, acute renal failure, hematuria, abnormal liver enzymes	Normal complement, positive ANCA, anti-PR3, and anti-MPO No renal biopsy as creatinine improved with antibiotics (considered possible localized-renal ANCA vasculitis)	*B. henselae* IgG 1:32768, IgM <1:20 *B. quintana* IgG 1:16384, IgM <1:20 *C. burnetii* IgG phase II 1:512	*Bartonella* PCR positive from valve, negative from blood	Vegetation in the aortic valve with new severe valvular insufficiency and root abscess Pathology: infective endocarditis (negative Warthin-Starry; sample collected during readmission)	6 weeks of doxycycline and rifampin	Initial improvement of symptoms and *Bartonella* IgG titers Considered not a surgical candidate, but readmitted later due to severe aortic insufficiency and heart failure, underwent aortic valve and root replacement with resolution of symptoms

Table 2. Continued

Patients	Age, Gender	Risk factors/ Comorbidities	Time of Illness (weeks)	Clinical Presentation	Laboratory/Imaging	Immunology Testing/ Renal Biopsy	*Bartonella* Serology/ *Coxiella burnetii* Testing	*Bartonella* PCR Testing	Echocardiogram Findings/ Pathology	Management	Outcome
Patient 5	80, female	Prosthetic aortic valve due to aortic stenosis, cat exposure	43	Fever, malaise, weakness, weight loss	Pancytopenia, splenomegaly	Positive RF and ANA; complement and ANCA not tested	*B. henselae* IgG 1:262,144, IgM 1:320 WB positive for *B. henselae* *C. burnetii* phase I IgG 1:1024, phase II IgG 1:512; *Coxiella* PCR negative	*Bartonella* PCR negative in blood	Thickening of mitral and aortic valve	6 weeks of doxycycline and gentamicin	Resolution/ improvement of symptoms and pancytopenia
Patient 6	77, female	Prosthetic mitral valve due to ischemic mitral regurgitation, CKD, chronic low-dose steroid use for presumed PMR, steroid-induced DM, cat exposure	13	Fever, malaise, dyspnea, weakness, weight loss	Pancytopenia, acute renal failure requiring hemodialysis	Negative ANCA, low complements Renal biopsy: ATN and MPGN secondary to IE	*B. henselae* IgG 1:1024, IgM 1:40 *B. quintana* IgG 1:128, IgM 1:160 *C. burnetii* was not tested	*Bartonella* PCR positive in blood	Vegetation in the mitral valve with stenosis	4 weeks of doxycycline, rifampin, and ceftriaxone	Death due to multiorgan failure before valvular surgery
Patient 7	62, male	DM, CABG for CAD, recent diagnosis of AIDS	8	Fever, malaise, weight loss	Anemia, neutropenia, abnormal liver enzymes	Complement and ANCA not tested	*B. henselae* IgG 1:128, IgM <1:20 *B. quintana* IgG 1:128, IgM <1:20 *C. burnetii* serology negative	*Bartonella* PCR negative in blood	Vegetation in the aortic valve	6 weeks of doxycycline, gentamicin, ampicillin	Resolution/ improvement of symptoms and neutropenia, no evidence of vegetation in repeat echocardiogram
Patient 8	47, male	HTN, OSA	13	Altered mental status	Left Thalamic emboli/ stroke	Complement and ANCA not tested	*B. henselae* IgG 1:256, IgM <1:20 *B. quintana* IgG 1:128, IgM <1:20 *C. burnetii* serology negative	*Bartonella* PCR negative in valve	Calcified mass on the posterior leaflet of the mitral valve Pathology: thrombotic vegetation with focal inflammation	6 weeks of doxycycline and ceftriaxone, 2 weeks of gentamicin; mitral valve repair with annuloplasty	No more embolic episodes
Patient 9	57, male	Prosthetic aortic valve due to RHD, CKD with a recent diagnosis of renal vasculitis on steroids, cat exposure	30	Fever, malaise, fatigue, headaches	Anemia, thrombocytopenia, abnormal liver enzymes, acute renal failure	Low complement, positive ANCA and anti-PR3, negative anti-MPO Renal biopsy: complex-mediated GN with C3 deposits and focal crescents secondary to IE, no ANCA vasculitis	*B. henselae* IgG 1:1024, IgM <1:20 *B. quintana* IgG 1:512, IgM <1:20 *C. burnetii* phase II IgG 1:256	*Bartonella* PCR negative in blood	Vegetation on the left cusp of the aortic valve	6 weeks of doxycycline and ceftriaxone, 2 weeks of gentamicin	Resolution/ improvement of symptoms, cytopenias, and renal dysfunction, without immunosuppressors
Patient 10	80, male	Prosthetic aortic valve due to aortic regurgitation, CKD, DM, renal ANCA vasculitis on RTX and PDN 2 years prior to admission	48	Fever, malaise, weakness, weight loss, altered mental status	Anemia, acute renal failure, acute right hemispheric embolic stroke, PET scan showing splenic FDG avidity concerning for embolic event in the spleen	Negative ANCA, normal complement Renal biopsy not performed	*B. henselae* IgG >1:1024, IgM <1:20 *B. quintana* IgG >1:1024, IgM <1:20 *C. burnetii* PCR negative	*Bartonella* PCR positive in blood	Vegetation in the aortic valve with paravalvular abscess	2 weeks of ceftriaxone, planned 6 weeks of rifampin and 6 months of doxycycline (no surgical candidate)	Improvement of symptoms and renal failure with antimicrobials, loss in follow-up

Table 2. Continued

Patients	Age, Gender	Risk factors/ Comorbidities	Time of Illness (weeks)	Clinical Presentation	Laboratory/Imaging	Immunology Testing/ Renal Biopsy	*Bartonella* Serology/ *Coxiella burnetii* Testing	*Bartonella* PCR Testing	Echocardiogram Findings/ Pathology	Management	Outcome
Patient 11	55, female	Prosthetic aortic and mitral valve due to RHD, pulmonary valve homograft, CKD due to ATN, possible APS on PDN and Plaquenil, cat exposure	52	Fever, fatigue, malaise, weight loss, volume overload	Anemia, thrombocytopenia, acute on chronic renal failure, abnormal liver enzymes, splenomegaly	Low complement, positive ANCA, positive anti-PR3, negative anti-MPO Renal biopsy not performed due to anticoagulation	*B. henselae* IgG: > 1:1024, IgM: >1:20 *B. quintana* IgG: 1:1024, IgM: <1:20 *C. burnetii* phase II IgG 1:128	*Bartonella* PCR positive in pulmonary valve tissue, negative in blood	Vegetation in the pulmonary artery and ventricular aspect of the pulmonary prosthesis with severe regurgitation Pathology: Nodular calcification with mild acute inflammation	9 weeks of doxycycline, 2 weeks of rifampin and ceftriaxone; tricuspid valve repair and pulmonary valve replacement	Death post-surgery due to multiorgan failure (fungemia due to *Candida tropicalis*, pneumonia)
Patient 12	44, male	Alcohol abuse, renal failure due to presumed renal vasculitis, receiving a short course of steroids without improvement, cat exposure	26	Fever, fatigue, night sweats, weight loss	Anemia, leukopenia, acute renal failure, hematuria, proteinuria, splenomegaly	Low complement, positive RF, ANCA, and anti-PR3, negative anti-MPO Renal biopsy: immune-complex focal proliferative GN, likely infection-related	*B. henselae* IgG >1:1024, IgM >1:20 *B. quintana* IgG >1:1024, IgM <1:20 *C. burnetii* phase II IgG 1:256	*B. henselae* PCR positive in explanted mitral valve, negative in blood	Vegetation on the atrial and ventricular aspect of the mitral valve with mild-moderate regurgitation	6 months of doxycycline, 2 weeks of gentamicin	Initial improvement of symptoms, but no improvement of cytopenias and renal failure Patient required readmission to another hospital months later for mitral valve replacement, presenting resolution of cytopenias and improvement of renal function
Patient 13	22, male	Prosthetic pulmonary valve due to tetralogy of Fallot complicated with pulmonary regurgitation, cat exposure	22	Fever, fatigue, malaise, night sweats, weight loss	Anemia, leukopenia, hepato-splenomegaly	Complement and ANCA not tested	*B. henselae* IgG >1:1024, IgM <1:20 *B. quintana* IgG >1:1024, IgM <1:20 *C. burnetii* phase II IgG 1:32	*Bartonella* sp PCR positive in explanted pulmonary valve, negative from blood	Thickening of the pulmonary prosthetic valve with moderate regurgitation Pathology: healing infective endocarditis with bacterial rods	4 months of doxycycline, 2 weeks of gentamicin	Initial improvement of symptoms and cytopenias Patient was re-admitted later due to septic emboli to the lung and possible paravalvular abscess requiring replacement of the pulmonary valve
Patient 14	56, male	Prosthetic aortic valve due to severe aortic regurgitation, dog and cat exposure	43	Right hemianopia, transient left-sided clumsiness	Anemia, brain emboli	Complement and ANCA not tested	*B. henselae* IgG 1:8192, IgM <1:20 *B. quintana* IgG 1:512, IgM <1:20 *C. burnetii* phase II IgG 1:64	*Bartonella* sp BRPCR from explanted valve (closely related with *B. henselae*), negative from blood	Vegetation on the aortic valve, with severe aortic regurgitation Pathology: active endocarditis with small bacterial rods consistent with *Bartonella* spp. (positive Warthin-Starry stain)	12 weeks of doxycycline, 2 weeks of rifampin; aortic valve replacement	Resolution/ improvement of symptoms, slow improvement of *Bartonella* IgG titers

Table 2. Continued

Patients	Age, Gender	Risk factors/ Comorbidities	Time of illness (weeks)	Clinical Presentation	Laboratory/Imaging	Immunology Testing/ Renal Biopsy	*Bartonella* Serology/ *Coxiella burnetii* Testing	*Bartonella* PCR Testing	Echocardiogram Findings/ Pathology	Management	Outcome
Patient 15	51, male	Prosthetic aortic valve due to bioaspid aortic valve, CKD, received PDN 20 mg daily for presumed renal vasculitis, cat exposure	26	Fatigue, malaise, dyspnea, extensive macular-purpuric rash in lower extremities	Anemia, acute on chronic renal failure requiring hemodialysis, hematuria, hepatosplenomegaly	Normal complement, positive ANCA and anti-PR3, negative anti-MPO, positive cryoglobulins III Renal biopsy: immune-complex focal proliferative GN likely infection-related	*B. henselae* IgG 1:32768, IgM <1:20, *B. quintana* IgG 1:128, IgM <1:20 *C. burnetii* negative serology	*Bartonella* sp BRPCR from explanted valve, negative from blood	New severe aortic regurgitation Pathology: healed infective endocarditis with chronic inflammation	12 weeks of doxycycline, 2 weeks of gentamicin Received plasmapheresis for management of cryoglobulinemia; aortic valve replacement	Resolution/ improvement of symptoms (except for kidney failure), slow improvement of *Bartonella* IgG titers
Patient 16	57, female	No comorbidities	30	Fever, malaise, weight loss, volume overload	Anemia, splenomegaly, embolic phenomena to the spleen	Complement and ANCA not tested	*B. henselae* IgG 1:4096, IgM <1:20 *B. quintana* IgG 1:128, IgM <1:20 *C. burnetii* phase II IgG 1:32	*B. quintana* PCR from explanted aortic valve (PCR not performed in blood)	Vegetations in the aortic and mitral valves with root and perivalvular abscesses, severe aortic insufficiency Pathology: healing endocarditis with colonies of bacteria and focal valve destruction	52 weeks of doxycycline, 2 weeks of gentamicin; aortic and mitral valve replacement and aortic root debridement with pericardial patch reconstruction	Resolution/ improvement of symptoms, slow improvement of *Bartonella* IgG titers

Abbreviations: AIDS, Acquired immunodeficiency syndrome; ANA, antinuclear antibody; ANCA, antineutrophil cytoplasmic antibodies; APS, antiphospholipid syndrome; ATN, acute tubular necrosis; AZA, Azathioprine; BRPCR, broad-range polymerase chain reaction; CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; CKD, chronic kidney disease; DM, diabetes mellitus; FDG, fluorodeoxyglucose; GN, glomerulonephritis; GPA, Granulomatosis with polyangiitis; HTN, hypertension; IE, infective endocarditis; Ig, immunoglobulin; MPO, myeloperoxidase antibody; MPGN, Mesangial proliferative glomerulonephritis; OSA, obstructive sleep apnea; PCR, polymerase chain reaction; PDN, prednisone; PET, positron emission tomography; PR3, proteinase 3 antibody; RF, rheumatoid factor; RHD, rheumatic heart disease; RTX, rituximab; WB, western blot (test performed at Hôpitaux Universitaires de Marseille Timone, Marseille, France).

endocarditis (PVE), 6 underwent valvular replacement, whereas 4 were treated medically. Of the 6 patients with native valve endocarditis, 3 underwent valve replacement, 1 underwent valve repair, and 2 were treated medically.

Outcomes at 1-year follow up were evaluated in 15 patients (Table 2). Six patients received combined surgical and medical management, with 5 of them presenting clinical improvement, improvement of antibody titers, and/or resolution of vegetation in follow-up echocardiogram. One patient died after receiving pulmonary valve replacement due to *Candida tropicalis* fungemia and hospital-acquired pneumonia. Of the 9 patients initially treated medically, 4 patients had good outcomes, and 4 were readmitted later (104 days [average] post-diagnosis of *Bartonella* endocarditis) for undergoing valvular replacement due to relapsed or persistent disease. One of the patients, who was initially managed medically, presented multiorgan failure and died before undergoing valvular replacement.

DISCUSSION

In this small cohort, the majority of patients with *Bartonella* endocarditis had prior prosthetic cardiac valves and presented with cytopenias, acute kidney failure associated with positive PR3-ANCA, and a wide range of *Bartonella* serology titers. Low mortality, especially when patients received combined medical and surgical treatment, was observed.

Bartonella spp are an important cause of culture-negative endocarditis. Known risk factors for *B henselae* endocarditis include pre-existing valvulopathy, prosthetic cardiac valves, and cat exposure [1, 7–9]. Risk factors for *B quintana* infection include homelessness, HIV, and alcohol use disorder [1, 7, 8, 10]. It is interesting to note that 2 patients (12.5%) did not have any of the commonly described risk factors for *Bartonella* endocarditis, suggesting that there may be other potential risk factors that have not been elucidated yet.

Clinically, our patients had an insidious process characterized by nonspecific symptoms, including fever, malaise, and weight loss. Consistent with prior reports [4, 7], embolic complications were frequent and likely related to the common involvement of left-sided cardiac valves. Anemia was almost uniformly found in our cohort; however, other cytopenias were also common. *Bartonella* species can infect multiple cells, including erythrocytes, endothelial cells, and hematopoietic progenitor cells inducing cytopenias by autoimmune hemolysis, immune-mediated cytopenias, or hemophagocytic lymphohistiocytosis [11–14].

Nine patients presented with acute renal failure or new worsening of chronic renal disease, with 6 of them presenting positive PR3-ANCA on admission. Three of these patients were misdiagnosed with vasculitis and received immunosuppressants before the diagnosis of bartonellosis. Renal dysfunction is frequent in patients with endocarditis due to *Bartonella*

and other etiologies; it can be secondary to prerenal azotemia, septic emboli, or immunological phenomena leading to glomerulonephritis [15–17]. In addition, ANCA positivity has been found in the range of 18%–43% in patients with culture-positive endocarditis commonly caused by *Staphylococcus* and *Streptococcus* species. In contrast, ANCA positivity has been described as high as 60% in patients with *Bartonella* endocarditis [18]. It has been postulated that epitopes at the surface of *Bartonella* spp could induce a molecular mimicry phenomenon, eliciting autoantibodies [18]. Therefore, we emphasize the importance of considering the diagnosis of *Bartonella* endocarditis in patients with risk factors presenting with renal failure and positive PR3-ANCA.

All patients had a serological diagnosis of *Bartonella* infection, but *Bartonella* IgG titers varied widely. Only 12 (75%) patients had the previously recommended cutoff value of 1:800 for the diagnosis of *Bartonella* endocarditis [19]. Despite that the rest of the patients had lower IgG titers, they had improvement or resolution of symptoms after receiving *Bartonella*-directed treatment. Wharthin-Starry was only positive in 1 of the 3 samples in which this stain was used, but available pathology was consistent with endocarditis. Similar to other publications [1], *Bartonella* PCR in blood was positive in a minority of patients (14.3%) but higher (70%) from explanted valves. There was no correlation between having higher IgG titers and positive blood PCR. As described in other reports, cross-reactivity with *C burnetii* serology was frequent, but titers were substantially lower compared with *Bartonella* IgG titers [20, 21]. Our patients with low *Bartonella* IgG titer had negative *Coxiella* test.

Patients frequently received combination therapy that included a prolonged course of doxycycline with or without another oral antibiotic and a parental antibiotic (gentamicin or ceftriaxone) for at least 2 weeks. In a prior report, the use of aminoglycoside for at least 2 weeks was associated with better outcomes compared with the regimens that did not include aminoglycosides [4]. Similarly, all our patients who received gentamicin for at least 2 weeks survived, but many of them also received surgery during the initial hospitalization or later.

Although some studies suggested that patients with *Bartonella* prosthetic valve endocarditis have better outcomes when receiving combined surgical and medical management [22, 23], it has been reported that medical treatment alone may be an option in those who are diagnosed early in the disease course [24]. Two of our patients with PVE (patient 5 and patient 9) had good outcomes after receiving only medical treatment. It is interesting to note that they were not younger or had a shorter duration of illness compared to other patients who required surgery. Further studies, including a larger number of patients with *Bartonella* PVE, may help to characterize which patients could be safely managed with medical treatment only.

Five of six patients who received initial combined surgical and medical treatment had good outcomes in comparison to the patients who received initial medical treatment only, where 4 of 9 had good outcome, but 4 presented relapse/persistent disease requiring unplanned surgery. There were no significant differences in the use of antibiotics or length of medical therapy in both groups. Only 2 patients (12.5%) died during the 12-month follow up. This mortality rate is similar to previous reports from France and Spain that reported overall mortality of 11.9% and 9.4%, respectively [4, 25].

CONCLUSIONS

In conclusion, our findings suggest suspecting a *Bartonella* infection as a potential etiology of BCNE, especially in patients with a prosthetic cardiac valve, relevant epidemiological exposures, and renal failure with positive PR3-ANCA. Further studies with a larger number of cases are needed to confirm these findings.

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