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Case report

Bartonella endocarditis in patients with right ventricle-to-pulmonary artery conduit: 2 case reports and literature review☆

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ABSTRACT

Bartonella species are Gram-negative bacilli and fastidious bacteria that can cause a number of clinical syndromes, including blood culture-negative infective endocarditis (IE). The two most commonly isolated species in humans are *Bartonella quintana,* the agent of trench fever, and *Bartonella henselae,* mostly known for causing cat scratch disease (Edouard et al., 2015 [1]; Edouard and Raoult, 2010 [2]). Both species also cause bacillary angiomatosis, primarily in immunocompromised patients (Edouard et al., 2015 [1]; Fournier et al., 2001 [3]). The risk of *B. henselae* IE is increased in patients with cardiac valvular disease and congenital heart disease (CHD) (Edouard and Raoult, 2010 [2]; Das et al., 2009 [4]; Abandeh et al., 2012 [5]; Ouellette et al., 2016 [6]; Hoffman et al., 2007 [7]; Georgievskaya et al., 2014 [8]). In this article, we detail two cases of *Bartonella* IE in patients with right ventricle-to-pulmonary artery (RV-PA) conduits who presented to our institution. We also perform a literature review on *Bartonella* IE in patients with a history of RV-PA conduit or pulmonary valve replacement.

Methods

The case presentations of two patients who were diagnosed with *B. henselae* IE at Bronson Children's Hospital (Kalamazoo, Michigan) are included. An English language literature review in PubMed was conducted in PubMed with keywords including "Bartonella", "endocarditis" and "congenital heart disease". There was no limit on the publication date and no age cut-offs for the patients. All articles meeting the search criteria were reviewed individually. Any data relating to IE in patients with RV-PA conduits or pulmonary valve replacement (including pulmonary homograft, allograft and Ross-related procedures) were compiled as depicted in Table 1. The table includes demographic data including patients' age, gender and underlying cardiac abnormalities. The presenting signs and symptoms are described. The table also details diagnostic study results, treatment including surgical intervention and anti-microbial therapy, and presence or absence of renal complications.

Case 1

The patient was a 9-year-old girl with partial 15q deletion, cerebral palsy and epilepsy. Her cardiac history was notable for dextro-transposition of the great arteries, ventricular septal defect (VSD) and pulmonic stenosis status post (s/p) Rastelli repair and right ventricle-to-pulmonary artery (RV-PA) conduit. She was admitted due to fatigue for more than 1 month and an elevated creatinine level of 2.4 mg/dL detected during outpatient evaluation. The parents reported decreased appetite within that time frame but denied any febrile episodes.

On admission, she appeared ill and vital signs showed tachycardia to 112 beats per minute. Physical exam revealed a sinus rhythm and a 3/6 systolic murmur best heard along the left sternal border. Repeat laboratory workup confirmed a creatinine of 2.4 mg/dL with a glomerular filtration rate (GFR) of 28.4 mL/min/1.73 m^2. Cardiology was consulted as the clinical picture was concerning for

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Table 1
Demographics, underlying cardiac abnormalities, presenting symptoms/signs, diagnostics, surgical intervention, antimicrobial therapy and renal complications in patients with a history RV-PA conduit or pulmonary valve replacement and confirmed *Bartonella* endocarditis.

Age/Sex	Underlying cardiac abnormalities	Presenting symptoms/Signs	Diagnostics	Surgical intervention	Anti-microbial therapy	Renal involvement
3 y/M[9]	TOF with pulmonary atresia s/p BT shunts and RV-PA conduit and bilateral PA stents	2 mo of fatigue +SEM, HSM	*B. henselae* - IgG ≥ 1:1024 - IgM ≥ 1:20 - Blood PCR (+) TTE, TEE: vegetation on RV-PA conduit valve	Replacement of RV-PA conduit and RPA stent placement	CTX/Azithromycin /Rifampin (8 wk)/Gent (2 wk) until surgery +CTX/Azithromycin/Rifampin (6 wk)	No
6 y/M[6]	ASD, VSD, Interrupted aortic arch & modified Norwood and Rastelli procedure with RV-PA conduit	3 mo of fevers, chest pain, SOB, fatigue +SEM, HSM	*B. henselae* - IgG > 1:128 - IgM > 1:32 - Vegetation PCR (+) TTE, TEE: Thickened conduit valve with multilobulated vegetation	Surgical replacement of infected valve and conduit	CTX/Doxy/Rifampin (6 wk), then Doxy monotherapy until surgery + 4 wk postop	Yes
9 y/F[9]	VSD, Dextro-transposition of great arteries, Pulmonic stenosis s/p Rastelli repair and RV-PA conduit	1 mo of fatigue Elevated Creatinine on outpatient workup +SEM	- *Bartonella* serum PCR (+) - *Bartonella* vegetation PCR (+) *B. henselae* - IgG ≥ 1:1024 - IgM ≥ 1:20 *B. quintana* - IgG ≥ 1:1024 - IgM < 1:20 TTE: vegetation on RV-PA conduit valve	Replacement of RV to PA conduit	Azithromycin (7d)/Rocephin (9d)/Rifampin (7d) until surgery + Doxy/Rifampicin (42d)	Yes
9 y/M[10]	TOF/RV-PA conduit and tricuspid valve repair	4 mo of fatigue, cough, fevers +SEM, HSM	*B. henselae* - IgG > 1:1024 TTE: Thickened tricuspid valve concerning for vegetations	None	Doxy/Gent/Rifampin/Cefepime (2 wk), then Cefepime/Doxy (6 wk total)	Yes
9 y/M[4]	Congenital aortic valve, subvalvular stenosis/Ross-Konno procedure	3 wk fever, chills, night sweats +SEM, massive splenomegaly	*B. henselae* - IgG 1:512 - IgM 1:16 - Vegetation PCR (+) ECHO: pulmonary valve with multiple echogenic vegetations	Surgical replacement of pulmonary homograft and conduit	CTX/Gent/Doxy (3 wk), then CTX/Rifampin/Doxy (3 wk). Doxy monotherapy (3 wk) postoperatively	No
10 y/F[11]	VSD, Pulmonary atresia with pulmonary valve homograft and RV-PA conduit	3 mo of fever and night sweats +SEM, HSM	*B. henselae* - IgG > 1:256 - Vegetation PCR (+) ECHO: Large vegetation on aortic valve	Surgical replacement of pulmonary artery homograft	Gent (4 wk)/Doxy (6 wk)	No
14 y/M[12]	Bicuspid aortic valve/ Ross procedure with pulmonary valve homograft	Recurrence of fever and malaise after 8 wk of CTX and Vanc Cardiac murmur	*B. henselae* - IgG 1:1024 - Vegetation PCR (+) TTE: Vegetation on pulmonary valve	Surgical replacement of pulmonary homograft	Doxy/Gent (2 wk), then Doxy monotherapy (4 wk)	No
14 y/M[13]	TOF s/p BT shunt and RV-PA conduit with Melody valve placement (pulmonic)	5 mo of fatigue, SOB, weight loss	*B. henselae* - IgG > 1:1024 - IgM > 1:32 - Vegetation PCR (+) TTE,TEE: thickened valve leaflets, increased gradient across Melody valve, no overt vegetations	Removal of Melody valve, placement of pulmonary artery homograft	CTX (6 wk)/Gent (2 wk)/Doxy (8 mo)	No
14 y/M[6]	Shone complex (AS, MS, coarctation of aorta)/Ross– Konno procedure, followed by Melody valve placement within the RV-PA conduit	3 mo of nausea, fatigue, night sweats, 45-lb weight loss +SEM, HSM, petechiae.	*B. henselae* - IgG > 1:1024 - IgM > 1:1024 - BM and vegetation PCR (+) TTE, TEE, ICE: no obvious vegetations	Surgical replacement of infected Melody valve and conduit	Doxy/Rifampin (2 wk), then doxy monotherapy until surgery + 10 d postop (3 mo total)	Yes
15 y/M[14]	Truncus arteriosus type II s/p pulmonary homograft with Melody valve (pulmonic)	Fever, abdominal pain and splenomegaly unknown duration	*B. henselae* - IgG/IgM (+) - Vegetation PCR (+) *B. quintana* - IgG/IgM (+) TTE: Increased echogenicity of pulmonic valve leaflets with vegetations	Removal of infected Melody valve, RVOT reconstruction with a pulmonary homograft	Vanc/Gent/Amoxicillin-clavulanate	None
18 y/F[15]	TOF s/p RV-PA conduit with bio-prosthetic pulmonic valve	3 mo of fatigue, intermittent fevers, 16-lb weight loss +SEM	*B. henselae* - IgG > 1:1024 - IgM > 1:64 - Blood PCR (+) TEE: No vegetations seen	None	Doxy/Rifampin (15 wk)	Yes
21 y/M[8]						Yes

(*continued on next page*)

Table 1 (*continued*)

Age/Sex	Underlying cardiac abnormalities	Presenting symptoms/Signs	Diagnostics	Surgical intervention	Anti-microbial therapy	Renal involvement
	Congenital aortic stenosis/Ross procedure with pulmonary artery homograft, followed by Melody valve placement (pulmonic)	4 mo of intermittent fever, fatigue, abdominal pain, weight loss. Splenomegaly on CT	*B. henselae* - IgG > 1:1024 - IgM (-) - Vegetation PCR (+) - Vegetation Warthin–Starry staining (+) TTE, TEE: No vegetation, increased gradient across Melody valve ICE: Vegetations on Melody valve	Removal of infected Melody valve	Doxy/Rifampin (6 wk), then Doxy monotherapy (6 mo)	
36 y/F[7]	VSD, ASD s/p closure Pulmonary atresia, dextrocardia and a double outlet RV s/p BT shunts (after birth) and Rastelli procedure with RV-PA conduit (13 y)	6 mo of intermittent fever, chills, and cough. +SEM	*B. henselae* - IgG ≥ 1:1024 - Blood PCR (+) - Vegetation PCR (+) - Vegetation Warthin–Starry staining (+) TTE: aortic valve vegetation TEE: RV-PA conduit vegetation	Removal of RV to PA conduit, insertion of an aortic homograft, AV replacement	Gent + CTX (1 wk), then Doxy + Gent (2 wk), then CTX + Doxy (6 wk), then Doxy (4 wk), then Cefpodox (brief)	No
42 y/M[5]	TOF s/p BT shunts, closure of VSD, RV-PA conduit, and reconstruction of both PA.	6 mo of fever, night sweats and weight loss. +SEM, splenomegaly	*B. henselae* - IgG ≥ 1: 16,384 - IgM ≤ 1:20 - Vegetation PCR (+) *B. quintana* - IgG ≥ 1:8192 - IgM ≤ 1:20 TEE, TEE: large vegetation within RV-PA conduit	Removal of Dacron graft/prosthetic valve and replacement with bioprosthetic valve/ bovine pericardial patch repair	CTX (6 wk), Doxy (6 wk), and Gent (2 wk)	No
49 y/F[22]	TOF s/p VSD closure with a patch and RVOT reconstruction, followed later by pulmonary valve replacement with a pulmonary homograft for severe PR, tricuspid annuloplasty for moderate TR, and closure of a residual VSD.	Several weeks of generalized abdominal discomfort, fatigue, fever, and exertional dyspnea. Prominent neck vein distention with Kussmaul's sign, +SEM +EDM	*B. quintana* - IgG ≥ 1:128 - IgM > 1:20 TTE: Large irregular mobile masses on the pulmonic valve, severe PR	Surgical replacement of the pulmonary valve with a 27-mm MedtronicFreestyle conduit and closure of residual VSD and PFO.	CTX + Doxy	No

AS: aortic stenosis. ASD: atrial septal defect. BM: bone marrow. BT: Blalock-Taussig. CT: computed tomography. CTX: ceftriaxone. d: day. Doxy: doxycycline. EDM: early diastolic murmur. F: female. GN: glomerulonephritis. HSM: hepatosplenomegaly. ICE: intracardiac echocardiogram. lb: pounds. M: male. mo: months. MS: mitral stenosis. PA: pulmonary artery. PR: pulmonary regurgitation. RV: right ventricle. RVOT: right ventricular outflow tract. SEM: systolic ejection murmur. SOB: shortness of breath. s/p: status post. TEE: transesophageal echocardiogram. TOF: tetralogy of Fallot. TR: tricuspid regurgitation. TTE: transthoracic echocardiogram. Vanc: vancomycin. VSD: ventral septal defect. wk: weeks. y: years old. (+): positive.
(+): positive.
(-): negative.

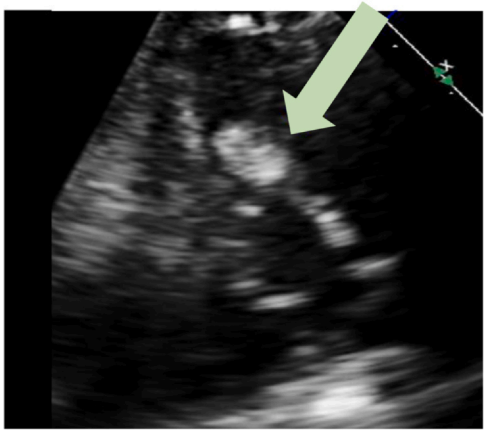

Fig. 1. Echocardiogram parasternal long axis view. The green block arrow indicates new vegetation on the conduit valve, measuring at 8 mm x 7 mm. The conduit leaflets also appeared significantly thickened. However, there was no conduit insufficiency. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

subacute bacterial endocarditis. An echocardiogram showed a significant change in the conduit valve with an echo-bright, mobile mass most consistent with a vegetation (Fig. 1). This vegetation was not seen on echocardiograms done 1.5 months and 8 months prior. Blood cultures were negative. Serological studies showed *B. henselae* IgG ≥ 1:1024 (reference range < 1:128) and IgM ≥ 1:20 (reference range < 1:20), *B. quintana* IgG ≥ 1:1024 (reference range < 1:128) and IgM < 1:20 (reference range < 1:20), and positive *Bartonella* serum polymerase chain reaction (PCR). Her contact history was positive for exposure to a stray cat and its kittens that her family had taken in for about 6 weeks, with the exposure occurring about 6 months prior to the patient's presentation for IE. She was started on a regimen of ceftriaxone, azithromycin and rifampin. Despite a normal renal ultrasound, her kidney function continued to worsen. Her complement 3 (C3) and C4 were 26 mg/dL (reference rage of 86–184 mg/dL) and 9 mg/dL (reference range 24–59 mg/dL), respectively. This was suggestive of hypocomplementemic glomerulonephritis secondary to infective endocarditis. She was subsequently transferred to a quaternary center for further management.

The infected RV-PA conduit was replaced with a 24 mm pulmonary homograft and a 24 mm Hemashield graft. She completed a

42-day course of treatment with doxycycline and rifampin. Although her renal function improved over time, she developed hypertension as a result of the kidney injury necessitating ambulatory pediatric nephrology follow up.

Case 2

The patient was a 3-year-old boy with tetralogy of Fallot (TOF), pulmonary atresia and VSD s/p Blalock-Taussig shunt, RV-PA conduit and bilateral pulmonary artery (PA) stents. During routine follow up, an echocardiogram found bilateral in-stent stenosis and a thickened and irregular RV-PA conduit valve with a flail posterior leaflet. The presence of a vegetation could not be ruled out. Meanwhile, neither the patient nor the parents reported any symptoms. Given the concern for IE and bilateral PA stent stenosis, he was admitted. After evaluation by ophthalmology and infectious disease (ID) teams, clinical suspicion for IE was deemed to be minimal. He underwent cardiac catheterization with balloon angioplasty of the PAs without complication and was discharged in stable condition. Four months later, a repeat echocardiogram found not only the thickened conduit valve, unchanged from previous study, but also an echogenic and mobile mass on the posterior leaflet consistent with possible vegetation (Fig. 2). His parents reported occasional fatigue and fever over the prior 2 months. He was admitted for further evaluation of possible IE. Physical exam revealed a new hepatosplenomegaly (HSM). During this 3-day hospital admission, his clinical status was stable, and the ID team decided to pursue laboratory evaluation prior to initiating any antibiotic treatment. Results yielded *B. henselae* IgG ≥ 1:1024 and IgM < 1:20, *B. quintana* IgG ≥ 1:1024 and IgM < 1:20, and negative serum PCR. No antimicrobial treatment was given due to negative serum *Bartonella* PCR and negative IgM titers, and the echogenic mobile mass was deemed to be a sterile vegetation. Two months later, another heart catherization was performed to further evaluate patency of his PA stents. An echocardiogram at the referral center noted a mobile and echogenic focus seen near the origin of the left PA, again raising suspicion for a vegetation. Considering the continued presence of the vegetation and unresolved HSM on physical exam, patient was again admitted and started on ceftriaxone, gentamicin, azithromycin and rifampin. Repeat studies showed *B. henselae* IgG ≥ 1:1024 and IgM ≥ 1:20, and *B. quintana* IgG < 1:128 and IgM < 1:20. In this admission, serum *Bartonella* PCR was positive.

His contact history was positive for exposure to the family pet cat that passed away 1 year prior to his presentation for IE, with no further exposure to cats thereafter. His regimen was tailored to 2 weeks of gentamicin, and ceftriaxone/azithromycin/rifampin continued until surgery. Due to his age, doxycycline was held due to risk of permanent teeth discoloration. Three months after this admission, he had his RV-PA conduit replaced with a 24 mm pulmonary homograft. He was continued on ceftriaxone/azithromycin/rifampin for another 6 weeks post-surgery. His hepatosplenomegaly had resolved on follow-up examination.

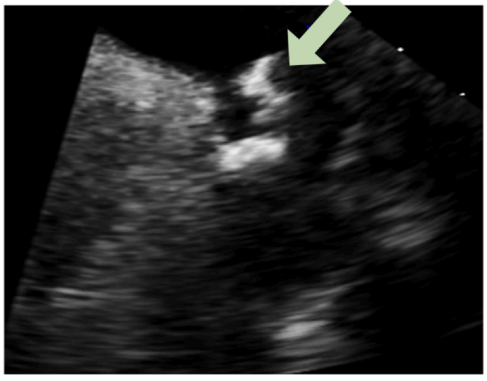

Fig. 2. Echocardiogram parasternal view. The green block arrow indicates an extremely thickened conduit valve. Also, not shown is an additional mobile echogenic focus, which may be valve tissue, thrombus or vegetation. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Results

Altogether, fifteen patients were identified to have a history of either RV-PA conduit, pulmonary homograft and Ross procedure (including Ross-Konno procedure). Other CHDs are also mentioned, including tetralogy of Fallot (TOF), ventricular septal defect (VSD) and atrial septal defect (ASD). The patients' clinical courses were also reviewed for not only the chief complaints, but also the duration of symptoms. Notable physical examination findings such as hepatosplenomegaly and systolic ejection murmur are reported. For the diagnosis, we collected information regarding echocardiogram findings and *Bartonella* evaluation. If not mentioned, the echocardiogram is simply listed as ECHO; otherwise, it is specified as transthoracic (TTE), transesophageal (TEE) or intracardial echocardiogram. Diagnosis of *Bartonella* is confirmed with serum antibody (IgG and IgM), PCR testing, and Warthin–Starry tissue stains. PCR was performed on different tissue sources, including vegetation, blood and bone marrow. If available, surgical interventions are described. Similarly, the anti-microbial regimen represents both the therapeutic agent and the length of treatment. Last, renal complications are detailed.

Discussion

Bartonella species are an important cause of culture-negative IE with reported risk factors being alcoholism, houseless status, and pre-existing valvular disease [1–3]. In fact, the association between *Bartonella* endocarditis and patients with valvulopathy has been well established and this phenomenon is seen in both the pediatric and adult populations [3,6,16]. Ouelette et al. described 10 cases of *Bartonella* endocarditis in patients with CHDs, several of whom had IE involving RV-PA conduits or the pulmonary valve. Pulmonary valve endocarditis in a structurally normal heart is rare, occurring in less than 1.5–2.0% of patients diagnosed with infective endocarditis [17]. The increased incidence of pulmonary valvular IE in patients with complex congenital heart disease is likely subsequent to the inherent pulmonary valvulopathy and use of prosthetic material in pulmonary valve replacement procedures in this subset of patients [6]. Driven by two patients with a history of RA-PV conduits who were found to have *Bartonella* IE at our institution, we sought to review the literature on reported cases of Bartonella IE in patient with complex CHDs. We found 15 published cases of patients with CHDs with RV-PA conduit or pulmonary valve replacement and a history of *Bartonella* endocarditis [4–15,18]. Including the two described cases as above, we have a total of 17 patients. All of these patients had a history of cardiac surgery. Furthermore, the presence of a RV-PA conduit is seen in 14 out of 17 cases. Among the 15 patients, the age ranges from 3 to 49, with a median age of 14 years. Eleven out of the 15 patients are of the pediatric age group (age 18 years and below). The male to female ratio is 10–5. The common CHD observed is TOF, seen in 6 patients.

Clinical presentations of *Bartonella* IE comprise of mostly non-specific signs and symptoms. Prolonged fever, often for month, was seen in 13 of 15 cases (87%) along with fatigue (60%), weight loss (33%) and night sweats (27%). Other clinical features include chest pain, shortness of breath, cough and chills. A murmur, especially a systolic ejection murmur, is reported in 11 cases (73%), although the timing of onset of these murmurs is often difficult to establish. Hepato- and/or splenomegaly on physical exam or CT imaging is

noted in 9 of 15 cases (60%). The insidious and prolonged nature of symptoms makes it imperative to have a high index of suspicion for IE when evaluating patients with CHD presenting with vague complaints.

In addition to the nonspecific clinical picture, diagnosis of *Bartonella* IE can be challenging and is made based on the modified Duke criteria [19]. TTE is the initial imaging modality for investigation of IE, due to its rapid and non-invasive nature and its usefulness in evaluating for anterior cardiac abscesses and valvular dysfunction [20]. TEE still offers higher sensitivity and specificity for detection of vegetation [21]. However, as highlighted in Case 2, confirming the presence of a vegetation via TTE and TEE is not always straightforward. This challenge has been reported in other studies and detailed in Table 1 [6,13,15]. In other words, the evaluation of IE in patients with high clinical suspicion should continue even in the absence of vegetations on echocardiography.

Bartonella species are fastidious gram-negative organisms rarely demonstrating growth. As blood cultures are often negative, the most effective diagnostic strategy combines serologic testing and direct polymerase chain reaction (PCR) from vegetations or valve specimens when available. *B. henselae* IgG ranges between 1:128 to 1:16,384, with an average of 1:2038. Houpikian and Raoult established that an IgG antibody titer to *Bartonella* species at or above 1:800 is 95.5% predictive of *Bartonella* IE [16]. Nine out of 15 patients in our study had *B. henselae* IgG titer above 1:800. *B. quintana* was isolated in three patients. Three patients with IgG less than 1:800 had vegetation samples that tested positive for *Bartonella* via PCR. PCR testing of valvular tissues is recommended to provide stronger diagnostic evidence. Overall, 80% of the cases had positive *Bartonella* PCR result from their vegetations. Three patients had positive serum PCR for *Bartonella* and one had positive PCR of bone marrow tissue.

The treatment plan typically involves surgery and antibiotics. Two patients did not receive any surgical intervention [10,15]. The rest underwent replacement of their RV-PA conduits and/or removal of their infected valves. Antibacterial therapy was given to all patients. The standard treatment for documented *Bartonella* IE includes doxycycline for 6 weeks and gentamicin for 2 weeks [22]. Yet, as detailed in Table 1, both the therapeutic agents and duration of treatment vary widely. This is likely driven by a number of factors, some of which include patient's age, challenges with diagnosis, time between diagnosis and surgical intervention. More studies are needed to better define the optimal treatment approach.

Physicians should also be aware of the extracardiac involvement of IE, most notably renal abnormalities. Associated conditions include perinephric abscess, emboli causing renal infarction and immunologic phenomenon, specifically hypocomplementemic glomerulonephritis [6,22]. In Case 2, although the patient's *Bartonella* IE was diagnosed and treated promptly, her kidney injury from hypocomplementemic glomerulonephritis secondary to IE persisted for years. In total, six of 15 (40%) patients developed renal complications.

Conclusion

Bartonella species have been established as a cause of blood culture-negative infective endocarditis with a reported risk factor of known valvular heart disease. In this study, we report two cases in our institution of *Bartonella* endocarditis with a history of RV-PA conduits and a literature review of patients with RV-PA conduits or pulmonary valve replacement and *Bartonella* endocarditis. In total, we have 17 such patients, of which 14 had an RV-PA conduit. This study highlights the importance of keeping *Bartonella* IE in the differential for patients presenting with prolonged and nonspecific signs and symptoms, especially in the subset of CHD patients with RV-PA conduits, in spite of absence of vegetations on echocardiography. Diagnosis combines echocardiogram findings, serologic testing and tissue/serum *Bartonella* PCR. Treatment involves surgical intervention and prolonged antibacterial therapy. Further research and data are needed to establish a standardized treatment approach in those with CHD, most notably RV-PA conduits, and *Bartonella* endocarditis.

Ethical approval

Not applicable.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contribution

Haripriya Santhanam: Study design, data collection, data analysis, writing, review of manuscript. Minh H.N. Nguyen: Study design, data collection, data analysis, writing, review of manuscript. Nirmal Muthukumarasamy: Study design, data collection, data analysis, writing, review of manuscript. Aditya Mehta: Study design, data collection, data analysis, writing, review of manuscript. Michael T. Francisco: Study design, data collection, dataanalysis, writing, review of manuscript. Robin R. Fountain: Writing, review of manuscript. Nicholas J. Helmstetter: Writing, review of manuscript.

Conflict of Interest

None.

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