

# *Bartonella* endocarditis in a child with tetralogy of Fallot complicated by PR3-ANCA positive serology, autoimmune hemolytic anemia, and acute kidney injury

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## Key Clinical Message

Although the role of ANCA in infective endocarditis is unclear, *Bartonella henselae* has been implicated as the culprit in cases of PR3-ANCA positive subacute bacterial endocarditis (SBE) with glomerulonephritis. In this case, a Coombs-positive autoimmune hemolytic anemia and glomerulonephritis accompanied a PR3-ANCA positive SBE caused by *Bartonella henselae*.

## KEYWORDS

cardiovascular disorders, hematology, infectious diseases, pediatrics and adolescent medicine

## 1 | INTRODUCTION

A 10-year-old male with a history of tetralogy of Fallot and pulmonary valve replacement presented with 2 weeks of decreased energy and intermittent fevers. Examination and transthoracic echocardiogram TTE confirmed endocarditis. Laboratories revealed glomerulonephritis with elevated cytoplasmic staining antineutrophil cytoplasmic antibodies (cANCA) and anti-PR3 antibody. During treatment, serological assays showed an elevated *Bartonella henselae* IgG titer and further history revealed multiple, new cat scratches. Persistent anemia unresponsive to EPO and iron was found to be Coombs test positive and hemolytic. The patient recovered after prolonged antibiotic treatment and replacement of the pulmonary valve. *Bartonella* SBE in a child with underlying congenital heart disease may cause PR3-ANCA positivity with both progressive glomerulonephritis and other immune-mediated processes such as a Coombs-positive autoimmune hemolytic anemia.

*Bartonella henselae* is a gram-negative rod that causes cat scratch disease, a syndrome characterized by fever and regional lymphadenopathy most commonly seen in children with a recent bite or scratch by a cat. *B. henselae* is a known cause of culture-negative endocarditis and has recently been

implicated in cases of endocarditis with atypical features. In one case, *B. henselae* was confused with a granulomatosis with polyangiitis (GPA) due to elevated c-ANCA and anti-PR3 antibody in a 28-year-old with endocarditis of a bicuspid aortic valve.<sup>1</sup> Further, this organism has been identified as the causative agent in a growing number of cases of PR3-ANCA positive subacute bacterial endocarditis (SBE) with accompanying glomerulonephritis.<sup>2-5</sup> Although hematologic manifestations are rare, generalized *Bartonella* infection has induced an autoimmune hemolytic anemia in at least one case.<sup>6</sup> Considering *Bartonella*'s association with PR3-ANCA positive infective endocarditis (IE), other immune-mediated syndromes could accompany this infection. To our knowledge, this is the first described case of *Bartonella* SBE in a child with underlying congenital heart disease causing PR3-ANCA positivity complicated by both progressive glomerulonephritis and a Coombs-positive autoimmune hemolytic anemia.

## 2 | CASE

A 10-year-old male with a history of tetralogy of Fallot (repaired in infancy), followed by pulmonary valve

replacement (19 mm pulmonary homograft) 1 year prior to presentation, complained of 2 weeks of decreased energy and intermittent fevers of 38.8–39.4°C. Although he initially reported to cardiology clinic for scheduled removal of a fractured sternal wire, he appeared unable to undergo the removal. His vital signs on admission were the following: temperature 37.1°C, blood pressure 106/79 mm Hg, respiratory rate 18 breaths per minute, and heart rate 81 beats per minute. Despite his admission temperature, his mother reported fevers that usually appeared at night. His exam was remarkable for a pale complexion, a 1/6 systolic murmur, and mild splenomegaly. There were no identifiable splinter hemorrhages, Roth spots, Osler's nodes, or Janeway lesions.

The patient's white blood cell count was  $5.7 \times 10^9$  per liter (L) (48% neutrophils, 44% lymphocytes, and 4% monocytes) (normal:  $3.4\text{--}9.5 \times 10^9/\text{L}$ ), his hemoglobin was 6.9 g/dL (normal: 12.0–14.0 g/dL), mean corpuscular volume was 81.1 fL (normal: 80–96 fL), and his platelet count was  $113\,000 \times 10^9/\text{L}$  (normal:  $150\,000\text{--}450\,000 \times 10^9/\text{L}$ ). Complete metabolic panel was notable for a blood urea nitrogen and creatinine of 84 mg/dL (normal: 7–20 mg/dL) and 5.3 mg/dL (normal: 0.3–0.7 mg/dL), respectively. Haptoglobin and lactate dehydrogenase were normal. Urinalysis showed 3+ blood, 2+ protein, negative nitrites, negative leukocyte esterase, and positive granular casts. His C-reactive protein was elevated at 3.10 mg/L (normal <1.0 mg/L) and his erythrocyte sedimentation rate was elevated at 37 mm/h (normal: 3–13 mm/h). On admission, his cANCA was positive at a 1:40 titer (normal: negative).

A transthoracic echocardiogram (TTE) demonstrated thickening of the pulmonary homograft valve leaflets, with small vegetations. The right ventricle was mildly dilated and hypertrophied. There was evidence of trivial pulmonary stenosis with trivial pulmonary regurgitation. Chest x-ray showed a fractured 3rd sternal wire but was otherwise normal. Based on the findings, infectious endocarditis was suspected, and he was started on IV ceftriaxone without concurrent gentamicin due to his significant renal dysfunction. Clindamycin (IV) was added to cover oral anaerobic organisms and MRSA, and aspirin 81 mg was added for thromboprophylaxis. Despite his initial antibiotics, he continued to spike nightly fevers and multiple blood cultures remained no growth. He was subsequently changed to ampicillin/sulbactam and rifampin given AHA guidelines for childhood culture-negative endocarditis with avoidance of gentamicin. Twelve days after admission, IgG antibodies returned positive for *Bartonella henselae* infection at a 1:2560 titer (current or previous infection: IgG titer: >1:128). On further history, he indicated that he had numerous cats at home as well as a new kitten that had scratched him multiple times over the past month. Due to serology and clinical suspicion, antibiotics were adjusted

to rifampin and oral doxycycline for presumed *Bartonella* endocarditis. A follow-up TTE showed persistent vegetations on the pulmonary valve, and the decision was made to move forward with surgical pulmonary valve replacement once a decrease in his *Bartonella* titers was documented.

The patient's initial abnormal renal function and elevated cANCA were accompanied by progressive hypertension throughout his clinical course. His GFR by modified Schwartz formula was 17 mL/min/1.73 m<sup>2</sup> (normal >60 mL/min/1.73 m<sup>2</sup>). An abdominal ultrasound revealed splenomegaly and enlarged, echogenic kidneys. His kidney function slowly improved throughout his course, but his blood pressure required up to four antihypertensives (amlodipine, hydralazine, lisinopril, and clonidine) to maintain adequate control. He was found to have hypocomplementemia with C3 of 46 mg/dL (80–170 mg/dL normal), and C4 of 5 mg/dL (14–44 mg/dL normal).

His microcytic anemia was initially treated with blood transfusions. He was also started on three times weekly erythropoietin injections (4000 Units) and three times daily iron supplementation. Despite treatment, he continued to have a slowly decreasing hemoglobin following transfusions. Further workup revealed reticulocytosis, with numerous spherocytes on admission CBC and CBCs drawn prior to transfusions. Although normal on admission, his lactic acid dehydrogenase (LDH) 2 weeks later was elevated at 332 units per liter (normal: 60–170 units/L). A Coombs test also returned positive 2 weeks after admission. There were no schistocytes or RBC fragments to suggest mechanical hemolysis. The presence of reticulocytosis, elevated LDH, spherocytes, and Coombs positivity, suggested an autoimmune hemolytic anemia (AIHA) as the cause of his hemoglobin abnormalities throughout his clinical course. Following prednisone treatment, the anemia resolved. His mild splenomegaly also resolved following a course of prednisone.

### 3 | FOLLOW UP

Two months after hospitalization, his renal function continued to normalize as evidenced by improvements in GFR and hypertension. Additionally, he had some slight improvement in cANCA titer at 1:20. However, his *B. henselae* IgG titer remained >1:2560 titer. His pulmonary valve was replaced with a 23 mm pulmonary homograft. Prior to his surgery, he remained on monotherapy with doxycycline. The infected pulmonary homograft leaflet and main pulmonary artery were sent for pathology, microbiology, and DNA testing. Gross pathology of the pulmonary valve revealed multiple fragments of pink-tan and white vascular and cardiac valve pieces. Areas of white dystrophic calcification were identified adjacent to the presumed valve leaflets. Microscopic examination

revealed poorly vascularized fibrous connective tissue and thin amorphous foreign material. A few vessels were partially surrounded by inflammatory cells, lymphocytes, and macrophages containing granular material consistent with iron. *B. henselae* PCR of the pulmonary valve leaflet was negative. Following his surgery, he was resumed on dual therapy with doxycycline and rifampin. He had significant improvement in *B. henselae* titer on follow up after pulmonary valve replacement; his *B. henselae* IgG titer was 1:640 a little over a month from surgery. His renal function also continued to improve: his estimated GFR by modified Schwartz formula rose to 95 mL/min/1.73 m<sup>2</sup>. Long-term antibiotic plans were to continue rifampin for 6 weeks following surgery and doxycycline for 3 months after surgery.

## 4 | DISCUSSION

Our patient's initial presentation met Duke criteria for endocarditis given transthoracic evidence of pulmonary valve vegetation, fever during hospitalization, immunologic phenomena (glomerulonephritis), and serologic evidence of acute infection. According to the CDC, the diagnosis of *Bartonella* endocarditis can be made by serology or PCR analysis of infected tissue. A *B. henselae* IgG titer of >1:128 is sufficient evidence for current or previous disease. A documented rise in IgG titer during illness is sufficient for a current infection diagnosis. Our patient's *B. henselae* IgG titer did not rise during treatment but was associated with a history of a high exposure environment, and a decline in titer following antibiotic therapy and valve replacement. Our patient's *Bartonella* IgG titer was elevated while he had a normal *Bartonella* IgM. Bergmans et al<sup>7</sup> mentions how the course of cat scratch disease does not follow usual immunologic understanding, with some patients producing high IgM titers, some producing high IgG, and a few producing low levels of antibodies. Ultimate examination of the infected pulmonary valve leaflets with gross and microscopic pathology as well as *Bartonella* PCR sent from the tissue were negative. Compared with a non-*Bartonella* SBE group, Lepidi et al<sup>8</sup> illustrated that *Bartonella* endocarditis infected valves commonly have minimal vegetations and instead demonstrate fibrosis and calcification. Furthermore, he was on antibiotics months before his valve replacement, which may have interfered with isolation of the organism.

Culture-negative subacute bacterial endocarditis can occasionally be associated with ANCA, but its role remains elusive. In 1991, Wagner et al<sup>9</sup> showed that the association of vasculitis and endocarditis could be related to the presence of ANCA. Inflammatory diseases like infective endocarditis may lead to neutrophilic dysfunction and subsequent leakage of cytoplasmic PR3 or MPO. B-cell activation to neutrophilic contents results in blood vessel

damage and manifestations of vasculitis. We suspect that culture-negative endocarditis can cause B-cell activation and autoimmunization resulting in ANCA formation, hypocomplementemic kidney injury resembling a systemic vasculitis, and a Coombs-positive hemolytic anemia. A recent review by Cervi et al<sup>10</sup> found three previous cases of infective endocarditis by *Bartonella* causing ANCA-related glomerulonephritis. In the cases of *Bartonella* infection, PR3-ANCA was markedly elevated and all three patients had a pauci-immune glomerulonephritis. One of the three cases showed other immunologic sequela including arthralgia/myalgia, hemoptysis, and a purpuric rash.

## 5 | CONCLUSION

The case presented is unique for the following reasons: (1) PR3-ANCA was present with infective endocarditis; (2) hypertension, hematuria, hypocomplementemia, and reduced GFR were consistent with glomerulonephritis; (3) A Coombs-positive hemolytic anemia was identified; (4) A positive *Bartonella henselae* IgG titer and history of recent cat scratches were present; (5) The IgG titer declined, and kidney function recovered following antibiotic therapy and valve replacement.

Few cases examine the development of glomerulonephritis in IE-associated vasculitis with ANCA. The development of glomerulonephritis during IE increases morbidity and mortality, and usually requires treatment with an immunosuppressive agent.<sup>11</sup> The diagnosis is often overlooked due to focus on the primary infection. Complicating matters, other immune pathology can present in patients with IE-associated vasculitis with ANCA. In our case, much focus was given to cardiovascular and renal sequela while the persistent anemia was initially attributed to endocarditis-related inflammation. A more extensive hematologic workup was explored after observing a failure of anemia resolution. Our case lends further support for *Bartonella's* role as a cause of PR3-ANCA positive infective endocarditis with resultant immunologic effects. To our knowledge, a Coombs-positive hemolytic anemia has not been documented in relation to a *Bartonella henselae* caused PR3-ANCA positive infective endocarditis with glomerulonephritis. Cases like this suggest that clinical suspicion for *Bartonella* should be high when encountering endocarditis with atypical features.

## 6 | CLINICAL TAKEAWAYS

- Inflammatory conditions such as infective endocarditis can cause vasculitis with PR3-ANCA.
- Glomerulonephritis with PR3-ANCA appears to be the most common manifestation of this vasculitis.

- Other immune-mediated sequela such as an autoimmune hemolytic anemia, arthralgias/myalgias, skin rashes, hemoptysis and cerebral vasculitis are possible manifestations of IE with ANCA-related vasculitis.
- *Bartonella henselae* has been implicated as the causative agent in cases of PR3-ANCA positive infective endocarditis with glomerulonephritis and other immune processes.
- *Bartonella henselae* IE with PR3-ANCA can mimic other systemic vasculitides such as GPA.
- Clinical suspicion for *Bartonella* should be high when a patient presents with IE, PR3-ANCA positivity, glomerulonephritis, and/or other immune phenomena.

## CONFLICT OF INTEREST

None declared.

## AUTHORSHIP

JMW: analyzed and interpreted the patient data regarding the disease process and was the main author of the manuscript. All authors were involved in the care of the patient. All authors read and approved the final manuscript. MP: analyzed and interpreted cardiovascular data and was a major contributor in writing of the manuscript. JS: was instrumental in the conception and design of the report, interpretation of the disease process, and was a major contributor in the writing of the manuscript.

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