

Bartonella Infectious Endocarditis Associated With Cryoglobulinemia and Multifocal Proliferative Glomerulonephritis

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Bartonella sp. are a common cause of culture-negative infective endocarditis. Glomerulonephritis is a well-documented consequence of the immune activation associated with infective endocarditis. However, Cryoglobulinemia has not previously been reported in association with *Bartonella* infective endocarditis. Below we report a case of a 48-year-old male with *Bartonella henselae* infective endocarditis complicated by cryoglobulinemia and multifocal proliferative glomerulonephritis, highlighting a possible link between *Bartonella* sp. infection and type III cryoglobulinemia.

Keywords. Cryoglobulinemia; *Bartonella*; infective endocarditis; glomerulonephritis.

CASE REPORT

A 48-year-old male with a history of aortic insufficiency, bio-prosthetic aortic valve replacement, and complete atrioventricular block with a permanent pacemaker presented to the emergency room with progressive shortness of breath on exertion, night sweats, and an erythematous macular rash on his lower extremities. He lived in rural Pennsylvania with dogs and cats as pets and had recently been released from a 1-year period of incarceration, during which there had been multiple lice outbreaks. Physical examination was significant for a diastolic murmur. Laboratory studies revealed pancytopenia, paraproteinemia, and acute kidney injury; a urine analysis showed evidence of hematuria and proteinuria. Serum C3 and C4 levels

were low, and testing for HIV, hepatitis B and C (HBV, HCV), antinuclear antibodies (ANAs), rheumatoid factor (RF), and antineutrophil antibodies (ANCAs) was negative. Serum cryoglobulin screen was positive. Abdominal imaging showed no evidence of hydronephrosis or nephrolithiasis. Transesophageal echocardiogram demonstrated abnormal thickening of all the prosthetic leaflets and a mobile echo density attached to the right ventricular lead. Three sets of blood cultures off antibiotics were negative. Serologies for *Coxiella burnetii*, *Bartonella henselae*, and *quintana* as work-up for culture-negative endocarditis were sent. His serologies were positive for *Bartonella quintana* IgG (1:1024) and mildly positive IgM, and he was started on treatment with doxycycline and rifampin. Due to worsening renal function, he underwent a renal biopsy, which revealed cryoglobulinemia-associated multifocal proliferative glomerulonephritis (MPGN) with cellular crescents (Figures 1 and 2). Characterization of the cryoglobulins revealed a type III pattern. He received steroids and underwent plasmapheresis and was commenced on intermittent hemodialysis (iHD). Later serum DNA polymerase chain reaction (PCR), performed at Quest Diagnostics, was positive for *Bartonella henselae*. He underwent aortic valve replacement and pacemaker removal. 16 S ribosomal sequencing of the valve tissue, performed at the University of Washington, was positive for *B. henselae*. At 3-month follow-up, the patient was doing well and had stopped iHD.

DISCUSSION

Since initially being reported as a cause of endocarditis in 1993 [1, 2], *Bartonella* sp. have become increasingly appreciated as an etiology of culture-negative infective endocarditis (IE). Of the *Bartonella* sp., *B. quintana* is most commonly implicated in IE, followed by *B. henselae* [3]. Factors associated with *Bartonella* sp. infection include low socioeconomic status, homelessness, alcoholism, body louse infestation, contact with cats, and valvular disease [4]. Renal disease in the setting of IE is common and can be due to prerenal azotemia, septic emboli, or immunological phenomena leading to glomerulonephritis. In 1 case series, 40% of *Bartonella* patients had some degree of renal impairment; however, renal impairment due to glomerular disease is a rare occurrence. To date, there have been 11 reported cases of *Bartonella* IE with glomerulonephritis. Eight of these cases were ANCA induced [5]. However, Cryoglobulinemia with associated MPGN has not previously been reported in association with *Bartonella* IE. Mixed-type cryoglobulinemia (type II and II) results from chronic inflammatory states and has been linked to infectious pathogens, including chronic HCV and HBV infections and occasionally IE [6, 7]. Historical studies

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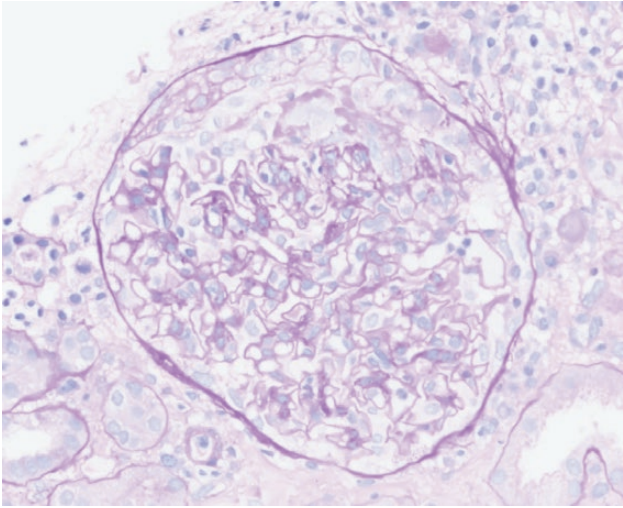


Figure 1. Renal biopsy with Periodic acid-Schiff staining demonstrating crescents.

that previously found a high prevalence of mixed cryoglobulinemia with IE did not include patients with *Bartonella* sp. due to lack of recognition of *Bartonella* as an implicating pathogen at the time [8].

Despite advances in our recognition of *Bartonella* sp. as a major cause of culture-negative IE, diagnosis remains challenging and requires a high index of suspicion. Due to its fastidious nature, the yield of standard culturing methods is low, and hence they are seldom relied on [9]. Serologies by enzyme-linked immunosorbent assay (ELISA) and indirect fluorescence antibody testing (IFA) have become reference methods. *Bartonella* titers >1:800 have been shown to have a high positive predictive value (95.5%) for IE; however, there are

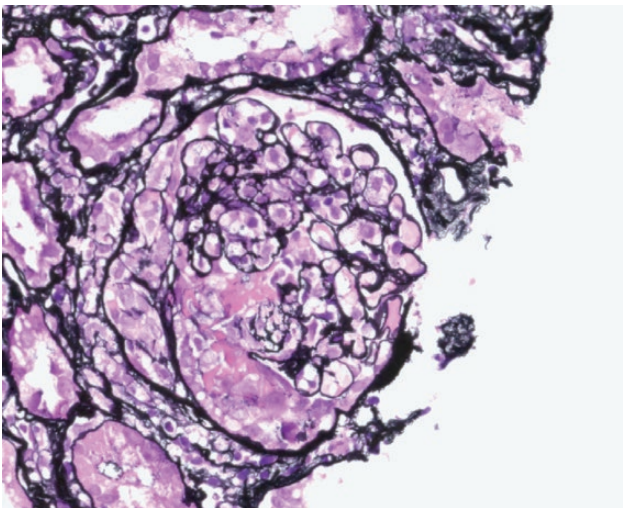


Figure 2. Renal biopsy with Jones staining demonstrating crescents and glomerular basement membrane breaks and duplication.

many limitations to serological testing [10]. *Bartonella* IgM is frequently negative (or low) in acute infection [10]. Also, there is frequent cross-reactivity across *Bartonella* species and with *C. burnetii* and *Chlamydia* spp., as in our case [10]. Serology can frequently be positive in both species. Advances in diagnostic DNA PCR amplification and 16S rRNA sequencing have made these diagnostic methods preferred given their high sensitivity and specificity, especially when applied to cardiac valve tissue, even in the setting of antibiotic therapy [11]. Robust prospective data to guide therapy in *Bartonella* IE are lacking. Current guidelines based upon expert panel opinion recommend 2 weeks of aminoglycoside therapy plus 6 weeks or more of doxycycline [12].

The above case of a 48-year-old male with valvular diseases and zoonotic exposure who later developed *Bartonella* infective endocarditis complicated by MPGN highlights a novel association between *Bartonella* infective endocarditis and type III cryoglobulinemia-induced glomerulonephritis. In future cases of endocarditis with glomerular disease where no contributing infectious etiology has been elucidated, *Bartonella* sp. infection should be considered, especially in the setting of classical risk factors.

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