Systemic Bartonellosis Manifesting With Endocarditis and Membranoproliferative Glomerulonephritis

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Abstract
Cat scratch disease caused by Bartonella species is mostly benign and self-limiting condition. Systemic infection is uncommon in immunocompetent host. We describe the case of a 66-year-old male who presented with sudden painless left eye blindness and brown-colored urine. Laboratory findings revealed progressively rising serum creatinine in association with nephrotic-range proteinuria at 7 g/day and glomerular hematuria on urinalysis. An echocardiogram demonstrated mitral and tricuspid valve vegetations despite multiple negative blood cultures. The left eye blindness was attributed to retinal artery occlusion from septic valvular embolus. Kidney biopsy showed membranoproliferative glomerulonephritis pattern of injury with “full house” pattern on immunofluorescent staining with subendothelial deposits on electron microscopy. Markedly elevated IgG (immunoglobulin G) titers for B henselae and B quintana were discovered. The patient had several cats at home. Kidney failure rapidly progressed to require hemodialysis. Once the diagnosis of systemic bartonellosis was confirmed, doxycycline (for 4 months) with rifampicin (for 3 months) were initiated. Repeat echocardiogram in 4 months demonstrated a resolution of valvular vegetations; however, the left eye blindness was permanent. In the present case the correct diagnosis of systemic bartonellosis allowed institution of appropriate antibiotic therapy and to also achieve a partial recovery of renal function and to discontinue hemodialysis.

Keywords
infectious endocarditis, membranoproliferative glomerulonephritis, systemic bartonellosis, culture negative endocarditis

Introduction
Cat scratch disease is an acute febrile illness with subacute regional lymphadenitis, most frequently caused by the organism Bartonella henselae. It is frequently benign and self-limiting. Systemic infection is uncommon in immunocompetent host. Bartonella species are fastidious gram-negative bacteria, which are known to cause vasculoproliferative lesions due to their specific tropism for endothelial cells and erythrocytes. Bartonella species were first recognized as endocarditis agents in 1993. B henselae or B quintana are responsible for most human cases of endocarditis and occurs in patients with preexisting abnormalities of the heart valves. We report the case of systemic bartonellosis manifesting with dialysis-dependent infection-associated glomerulonephritis (GN) and endocarditis that was successfully treated with prolonged antibacterial therapy. The majority of reported GN cases secondary to Bartonella endocarditis were pauci-immune GN with positive anti-neutrophil cytoplasmic antibodies (ANCA), while the current patient had negative ANCA serologies. Kidney biopsy showed membranoproliferative GN (MPGN) pattern of injury, which is rarely reported with Bartonella-associated GN.1

Case Report
A 66-year-old male presented initially in May 2019 with acute elevation of serum creatinine from baseline 0.8 mg/dL to 1.8 mg/dL in association with dysmorphic red blood cells and proteinuria (microalbumin/creatinine ratio, 647 mg/g). Prior to...
that presentation, the patient reported self-limited episode of cold-like symptoms and dark brown urine. The patient’s active medical problems included well-controlled hypertension, hyperlipidemia on statin, and Barret’s esophagitis on chronic proton pump inhibitor therapy. A physical examination was normal and laboratory workup was unrevealing (Table 1) at that time. The patient underwent cystoscopy with unremarkable findings. The patient underwent extensive serological workup, which was negative for hepatitis B and C, ANCA, anti-glomerular basement membrane antibody, antinuclear antibody, and anti-ds DNA antibody were also negative. Patient was closely followed in the renal clinic, his serum creatinine spontaneously improved to 1.2 mg/dL. In February 2020, the patient was admitted to the hospital after presented with sudden painless left eye blindness and recurrent brown-colored urine. A physical examination was notable for elevated blood pressure, new lower extremity edema, and complete loss of vision in the left eye. On dilated fundus examination, macula showed cherry red spot with whitening of surrounding tissue, characteristic manifestation of retinal artery occlusion. Optical coherence tomography displayed thickening of the tissue with edema but no cystic changes. Laboratory findings revealed progressively rising serum creatinine in association with nephrotic-range proteinuria at 7 g/day on a 24-hour urine collection and glomerular hematuria on urinalysis (Table 1). An echocardiogram demonstrated vegetations on tricuspid and mitral valves (Figure 1A). Multiple blood cultures were drawn but all returned negative.

Patient was started on intravenous pulse steroids for a suspicion of rapidly progressive GN and underwent a kidney biopsy, which showed MPGN pattern of injury with 14% cellular crescents on light microscopy. Immunofluorescent staining showed 3+ intensity granular staining in the mesangium and in the capillary loops for IgG, C3, C1q, and lambda. There was 2+ intensity staining in the same distribution for IgA and kappa light chains. There was a trace staining for IgM and C4 in the same distribution, and there was 4+ staining for total immunoglobulins. Subendothelial deposits with diffuse foot processes effacement were seen on electron microscopy (Figure 1B). Although repeat blood cultures remained negative, the constellation of valvular vegetations, left retinal artery occlusion, and kidney biopsy findings of MPGN-pattern suggestive of infection-associated GN led to further investigations of culture-negative endocarditis. In fact, markedly elevated IgG titers for B henselae and B quintana were discovered. Of note, the patient had several cats at home. Initially he was treated with empiric broad spectrum antibiotics and steroids, but kidney failure rapidly progressed to require hemodialysis. Once the diagnosis of systemic bartonellosis was confirmed, steroids were stopped and doxycycline (for the total course of 4 months) with rifampicin (for the total course of 3 months) were initiated. After 3 months of being dialysis-dependent, the patient was able to discontinue hemodialysis due to recovery of residual renal function with resolution of hematuria. The most recent SCr (serum creatinine) was 2.4 mg/dL. Repeat echocardiogram in 3

| Test                      | Nine months prior to acute presentation (May 2019) | August 2019 | Acute presentation (February 2020) | Four-month follow-up (May 2020) |
|---------------------------|---------------------------------------------------|-------------|-----------------------------------|---------------------------------|
| *Serum (normal values)*   |                                                   |             |                                   |                                 |
| Creatinine, mg/dL         | 1.8                                               | 1.2         | 3.5 and then became 8.3 within 1 week | 2.4                             |
| B. henselae IgG titer (<1:64) |                                                   |             |                                   |                                 |
| B. quintana IgG titer (<1:64) |                                                   |             |                                   |                                 |
| B. henselae and quintana DNA |                                                   |             |                                   |                                 |
| Complement C3 (80-190 mg/dL) | 121                                               | 80.8        |                                   |                                 |
| Complement C4 (16-47 mg/dL) | 24.2                                              | 10          |                                   |                                 |
| CH50 (31-60 U/mL)         | 25                                                |             |                                   |                                 |
| Cryoglobulin              | Not detected                                      | Not detected|                                   |                                 |
| Rheumatoid factor (0-15 IU/mL) | 17.4                                              | 29          | Not detected                      |                                 |
| Anti CCP IgG              |                                                   |             |                                   |                                 |
| Anti-DNASE B strep        | Negative                                          |             |                                   |                                 |
| Streptolysin O antibody   | Negative                                          |             |                                   |                                 |
| Brucella antibody         | Negative                                          |             |                                   |                                 |
| ENA panel                 | Negative                                          |             |                                   |                                 |
| HIV antibody              | Negative                                          |             |                                   |                                 |
| *Urine (normal values)*   |                                                   |             |                                   |                                 |
| Red blood cells (0-2/HPF) | >50                                               | 10-25       | >50                               | 3-5                             |
| White blood cells (0-2/HPF) | 0-2                                               | 0-2         | 6-10                              | 0-2                             |
| Microalbumin/creatinine ratio, mg/g (0-30) | 647                                               | 101         | 6066                              | 2994                            |

Abbreviations: IgG, immunoglobulin G; CH50, total hemolytic complement; CCP, cyclic citrullinated peptide; anti-DNASE B, anti-deoxyribonuclease B; ENA, extractable nuclear antigen; HIV, human immunodeficiency virus; HPF, high-power field.
months demonstrated a resolution of valvular vegetations; however, the left eye blindness, which was attributed to a septic valvular embolus was permanent.

**Final Diagnosis**
Systemic bartonellosis.

**Discussion**
Although blood culture–negative endocarditis is relatively uncommon (around 15% of endocarditis cases), *Bartonella* species are responsible for up to 28% of these cases. *Bartonella* endocarditis accounted for 3% of all cases of infective endocarditis in a study published by Raoult and colleagues. Surface adhesins are important factors for autoaggregation and biofilm formation by *Bartonella* species. Biofilm formation is a critical step in the formation of vegetative masses during *Bartonella*-mediated endocarditis and represents a potential reservoir for persistence by these bacteria. Other systemic manifestations of bartonellosis include ophthalmic involvement, such as neuroretinitis and conjunctivitis. Ophthalmic manifestations of the disease are usually self-limiting and benign. Visual recovery is often excellent, although severe vision loss has been reported. In the current case left eye blindness was permanent due to retinal artery occlusion from septic cardiac embolus. Diagnosis of *Bartonella* endocarditis is made by serological testing and polymerase chain reaction of blood and tissue samples; however, negative polymerase chain reaction does not exclude the active infection. IgG titer of $\geq 1:800$ has a positive predictive value of 95% in patients with infective endocarditis. Some data suggest a role for corticosteroids in infective endocarditis-related GN; however, in our case steroids did not appear to significantly change the renal disease course.

The spectrum of kidney lesions in infectious endocarditis is variable and includes direct consequence of infection, such as infarction from septic emboli, as well as lesions through immunologic mechanisms, such as ANCA-associated GN and immune complex–mediated GN. Antibiotics to treat the infection can also potentially cause renal injury due to interstitial nephritis. Patterns of immune complex deposition in immune complex–mediated GN includes classic postinfectious type with prominent IgG and C3 deposits, with electron microscopy-revealing subepithelial humps. Other reported immunofluorescence patterns include IgM dominant staining, IgA-dominant staining, and “full house” staining (positive immunofluorescent staining for IgM, IgG, IgA, C3, and C1q). Immunologic injury is thought to be primarily responsible for pathogenesis of endocarditis-associated GN, particularly in cases of immune complex–mediated disease. In patients with endocarditis, deposition of the circulating immune complexes leads to subendothelial deposits. In situ immune complex formation is another possible mechanism, likely secondary to implanted cationic bacterial antigens within the glomerular basement membrane.

GN is one of the minor criteria in the modified duke infective endocarditis criteria. In case series reporting causes of infection-related GN in adults, infectious endocarditis accounts for up to 6% to 20% of cases. The histopathology of endocarditis-associated GN can be variable: necrotizing and crescentic GN (53%) and endocapillary proliferative GN (37%) are the most common findings in contemporary investigations. The majority of reported GN cases secondary to *Bartonella* endocarditis were pauci-immune GN with positive ANCA, while MPGN pattern was extremely rare. It is important to highlight that MPGN pattern on kidney biopsy is a histological pattern that can be seen in heterogeneous conditions. Therefore, MPGN with negative workup for lymphoproliferative disorders, monoclonal gammopathies,
thrombotic microangiopathy, and usual infections should prompt clinicians to consider systemic infection with unusual pathogens. The treatment of infection-associated GN includes administration of appropriate prolonged antibiotic therapy for underlying infection. Multiple prior reports and recommendations have advocated the use of at least 2 antibiotics, one of them being an aminoglycoside (at least for the first 2 weeks of therapy), the second drug being a β-lactam, a macrolide, or a tetracycline for treatment of Bartonella endocarditis. A minimum of 4-week course of antibiotic therapy is usually recommended in a native valve disease and a minimum of 6 weeks of antibiotic therapy in prosthetic valve endocarditis. In the current case, aminoglycoside therapy was avoided due to renal failure. The role of steroids is controversial, and their use is not recommended.

Conclusions
Systemic bartonellosis is uncommon in immunocompetent individuals and could be difficult to suspect. In retrospect, the initial presentation of acute kidney injury and macroscopic hematuria in the current case were likely early renal manifestations of systemic bartonellosis. Cardiac valve involvement and septic retinal artery occlusion along with rapidly progressive GN leading to kidney failure and renal replacement therapy 8 months later were late dramatic manifestations of the disease. In the current case, the kidney biopsy was crucial for the correct diagnosis because of combination MPGN pattern of kidney injury and cardiac valve vegetations were classical for bacterial endocarditis and led to discovery of culture-negative endocarditis due to Bartonella. Institution of appropriate antibiotics therapy allowed a resolution of endocarditis and a partial recovery of renal function without need of dialysis.

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Ethics Approval
Our institution does not require ethical approval for reporting individual cases or case series.

Informed Consent
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