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Case report

A case of *Bartonella henselae* native valve endocarditis presenting with crescentic glomerulonephritis

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ABSTRACT

Bartonella endocarditis is often an elusive diagnosis, usually derived from evaluating multiple laboratory tests and assessment of presenting symptoms. Herein we describe a case of *Bartonella henselae* native mitral valve endocarditis with an initial presentation of volume overload and renal failure. The *Bartonella* organism is tedious to isolate from culture medium, causing most diagnoses to be delayed. Due to the destructive nature of *B. henselae* endocarditis, the need for rapid identification remains prudent. This therefore creates an opportunity for Next Generation Sequencing (NGS) to be used. We further summarize the varied presentations that may be associated with *B. henselae* endocarditis, and hope that this will heighten the clinicians' awareness of this entity when presented with acute onset renal failure and culture negative vegetations.

Introduction

From the flea's stomach to the human heart, *Bartonella henselae* remains elusive in its abilities and characteristics, rising in the ranks as one of the most common causes of culture negative endocarditis. They are fastidious, facultatively intracellular and pleomorphic gram-negative bacilli with the ability to evade culture detection and produce biofilms. The two species that predominantly stand out for causing culture negative endocarditis are *B. henselae* and *B. quintana*. *Bartonella*'s slow growing behavior and requirement for heme create a difficult environment for culture detection. Herein, we will describe a case of *Bartonella* endocarditis complicated by crescentic glomerulonephritis. We will review the pathogenesis of these infections, alternate presentations, diagnostic modalities and the currently available therapies.

Case report

65-year-old Caucasian male with a medical history significant for bicuspid aortic valve, childhood aortic valve procedure (patient was unable to clarify, but no prosthetic material) and first-degree heart block, who presented with progressive shortness of breath over a two month period. He had acute worsening two to three days prior to admission with a twenty-minute episode of chest pain day of admission. He recorded a 100.1 F temperature at home with chills. Other past medical history was notable for hyperlipidemia, prior stroke with residual right-sided deficit, 48-pack-year tobacco history, and a social history significant for both indoor and outdoor pets consisting of cats, dogs and birds. Vital signs at admission temperature 100.1 F, blood pressure 136/67, pulse 87, and oxygen saturation 99% on room air. Physical exam with bibasilar crackles with faint expiratory wheezing. A II/VI systolic crescendo–decrescendo murmur with radiation to the carotids was noted on auscultation with minimal lower extremity edema. Labs were remarkable for a white blood cell count of 4600 /uL, hemoglobin 9 g/dL, platelets 117,00 /uL, creatinine 1.95 mg/dL, normal liver function tests. SARS-CoV-2 RNA and influenza screens were negative. He was started on empiric pneumonia treatment with vancomycin, ceftriaxone and azithromycin. On hospital day 2, a transthoracic echocardiogram revealed mild to moderate mitral regurgitation with a mobile density of the anterior leaflet concerning for a vegetation. The aortic valve was not visualized well. One set of blood cultures was collected prior to antimicrobial initiation, eventually returning negative. That evening he developed acute tachycardia, hypotension and hypoxia. CT of the chest was obtained revealing peripheral ground-glass infiltrates with "crazy paving." He underwent a bronchoscopy with negative studies. Infectious disease was consulted on hospital day 3 for multifocal pneumonia as well as mitral valve findings. Blood cultures were obtained and were negative. Plasma Next Generation

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Table 1
Summary of diagnostic indices.

Blood cultures x3	Negative, only first set collected prior to antimicrobial administration
B. quintana, IgG with reflex titer	Positive, 1:512
B. quintana/B. henselae IgM	Negative
Bartonella henselae IgG with reflex titer	Positive, > / = 1:1024
Coxiella burnetti DNA	Not detected
Karius (Ref range < 10)	9653 DNA molecules per microliter
Brucella	IgG 3.02, detected. IgM not detected
Mitral Valve tissue pathology	Negative GMS stain for fungal organisms, Negative bacterial organisms
16s rDNA on valve tissue	Not done
Renal biopsy	Focal necrotizing and crescentic glomerulonephritis, immune complex type

Sequencing testing available on day 8 with 9653 DNA molecules per microliter (MPM) of *Bartonella henselae* detected. Given concern for *Bartonella* endocarditis, on hospital day 8 antimicrobials were changed to doxycycline and rifampin. *Bartonella quintana* and *Bartonella henselae* IgG testing positive with reflex titers of 1:512 and > / = 1:1024, respectively, and Brucella IgG positive at 3.02, all three available on day 9 (Table 1). Nephrology was consulted on day 5 secondary to progression of renal failure with creatinine rising to 2.13 mg/dL (prior normal creatinine). Given his pulmonary symptoms, autoimmune testing was completed on day 5 for anti-GMA, ANCA, and ANA negative, C3 and C4 borderline low at 80 mg/dL and 17 mg/dL, respectively. On day 9, renal biopsy was performed which showed focal necrotizing and crescentic glomerulonephritis. His renal function progressively worsened, but he remained non-oliguric. Renal dosed gentamicin was added to his therapy in place of rifampin on hospital day 17 after discussions with nephrology. That same day, he underwent a mitral valve replacement with intraoperative TEE noting stenotic mitral valve with central regurgitation, anterior and posterior leaflet thickening, and a bicuspid aortic valve with mild to moderate stenosis. Both mitral leaflets were excised, with the valve sent for pathology noting chronic inflammation, negative for fungal and bacterial organisms, as well as culture which was negative. Unfortunately, 16s rRNA sequencing from the valve was requested but not sent. Postoperative course was complicated by worsening renal failure requiring hemodialysis and hemorrhage requiring sternal exploration and washout. Gentamicin was discontinued after 14 days of therapy to assist with renal recovery. The patient remained on doxycycline 100 mg BID planned for 6 weeks of treatment post valve replacement. Unfortunately, he suffered a sudden PEA arrest, and expired on hospital day 34.

Discussion

Bartonella species are fastidious, intracellular, gram-negative organisms that reside within erythrocytes. Due to this unique predilection, *Bartonella* is known to inhabit two specific sites: the gut of bloodsucking arthropods and bloodstreams of mammalian hosts [1]. Cats have been identified as hosts when they become infected with *B. henselae* following the bite of infected fleas. *Bartonella* is transmitted to humans from a scratch (salivary contamination through grooming) or a bite from an infected cat. We reviewed 17 case reports from 2010 and 2020, 14 of those cases had contact with cats (Table 2).

Bartonella is a problematic organism to isolate from culture media. Blood cultures have as low as a 20% sensitivity [2]. Direct plating of blood or tissue is preferred with specialized agars (heart infusion, Trypticase soy, brucella agar, and Columbia agar supplemented with 5% hemoglobin) and incubated for up to 21 days. Special staining such as Warthin-Starry can be used but these are not specific for *Bartonella*. Serology seems to be the most informative. *B. henselae* IgG titers > 1:800 are considered to have the greatest sensitivity for endocarditis with positive predictive value of 0.955 [3]. Low level titers could indicate prior exposure to the bacteria or cross reactivity. IgM assays have lower sensitivity rates since assays react early in the disease process and wane after 10 weeks, but higher specificity than IgG [3]. False positive results may occur with *Coxiella burnetii* and *Chlamydophila pneumoniae*. PCR testing has been utilized on both serum and tissue with serum sensitivity is 33% and tissue sensitivity is 92%[4]. 16s rRNA from tissue is considered the gold standard, but is invasive. 16s rRNA requires the use of primers that are limited to a certain portion of the genome and thus do not always provide accurate results[5]. Usually, the diagnosis of bartonellosis involves several methods to corroborate the results.

Next Generation Sequencing (NGS) of microbial cell free DNA (mcfDNA) is a new and emerging diagnostic test. This method is noninvasive with a short turnaround time (28 h), detecting the normal products of bacterial turnover within the body. When we compare the turnaround time to serology, NGS and IFA are almost equal, adding in two to four days for NGS specimen shipping. As the test becomes more readily available, this should improve. The NGS test relies on sequencing mcfDNA in circulating plasma to identify over 1000 pathogens (including bacteria, fungi, viruses) and reports a quantitative amount as molecules per microliter (MPM). In one study, NGS reported a 95% sensitivity in culture positive endocarditis even with antimicrobial pre-treatment [3]. NGS was ordered for our patient given the expected low yield from routine blood cultures and to capture other fastidious organisms. From reflection of our case, the differential diagnoses were initially broad, therefore using NGS and IFA together helped secure a diagnosis. We used both tests to advocate for prompt surgical intervention. The downfalls to NGS are that it may pick up on low yield microbiota/viroma, requiring clinical interpretation [6] and average NGS costs are roughly twenty times more expensive than IFA. During literature review, it was noted that in some cases patients were left on doxycycline until IFA titers decreased. Serial NGS testing could be considered to evaluate pathogen levels and monitor responses, as down-trending MPM levels correlate directly with decreasing amounts of viable pathogen [7]. This topic however, needs further investigation and would prove to be useful especially since serial IgG levels overtime have been inconsistent [8].

Bartonella is the leading cause of culture negative endocarditis in the US [9] and second most common CNE pathogen worldwide [4]. The species typically infects native valves with the aortic valve being the most commonly reported [4]. Prosthetic valve infections have been described, with clinical presentations that are usually severe with rapid progression to heart failure. Rarely, cases of myocarditis associated with *B. henselae* and *B.quintana* infections have been reported. Some reports resulting in sudden unexpected cardiac death in previously healthy individuals [2]. About 70% of patients require valve replacement secondary to severity of valve damage [10]. Mortality remains low at 7% [10]. Various reviews of pathology found histologic findings such as fibrosis, endothelial proliferation and neovascular formation that were distinctive to *Bartonella* [11–13]. The suggestion is for higher calcification and less extensive vegetation material, indicating a more chronic inflammatory process [12]. These findings are supportive of the need for surgical intervention in addition to antimicrobials for clearance rather than medical management alone.

Renal failure is a common manifestation of *Bartonella* endocarditis, with one study estimating greater than 40% of patients present with such findings [14]. Specifically, rapidly progressive renal failure is noted to be a clinical feature in infection-associated glomerulonephritis (GN). Serology testing is typically done to rule out an autoimmune diagnosis in these instances; however, renal biopsy to assess for histological patterns appears to be of vital diagnostic value. Severe damage to the glomerular capillary walls results in crescent formation, findings that can be seen with immune

Table 2
Summary of prior case reports of Bartonella endocarditis.

	Age/Gender	Contact with cats	Pre-existing heart valve disorder	Valve involved	Other manifestations	Blood cultures	Bartonella serology by IFA	Autoimmune workup	Other testing (Karius, etc)	16 S Ribosomal DNA amplification and sequencing	Treatment: surgical, antimicrobials	Outcome
[22]	19 yo Male	Yes	Yes, bioprosthetic pulmonic valve	pulmonic	Crescentic glomerulonephritis (renal biopsy noting cellular crescent formation)	Negative after prolonged incubation	*B. henselae* 1:64,000	ANA 1:160, anti dsDNA > 1:20, decreased C3 69 mg/dL and C4 7.7 mg/dL. CRP 149 mg/L. Coombs positive, elevated haptoglobin 238 mg/dL	Not applicable	PCR assay targeting *B.henselae* ribC gene, and DNA sequencing on valve. Valve tissue not submitted for pathology for special staining.	Empiric antimicrobials: Vancomycin and Ceftriaxone on admission. Doxycycline added when blood cultures returned negative. Pulse dose solumedrol and hydroxychloroquine added for presume SLE diagnosis, stopped once trans-esophageal echocardiogram noted destruction of bioprosthetic valve, positive bartonella titer. Changed to Doxycycline and Rifampin; aminoglycoside not used secondary to ongoing renal failure. Prosthetic pulmonic valve replacement.	Repeat serology undefined time reduced to 1:800, renal function deterioration requiring peritoneal dialysis. ANA and anti-dsDNA antibodies, complement titers remained normal off immunomodulatory therapy
[23]	65 yo male	No, but home-less, alco-holism	Aortic and mitral regurgitation	Warts on AV and MV, moderate to severe AR	Cerebral aneurysm, vasculitis as noted by skin biopsy of purpura, crescentic glomerulonephritis	Multiple negative	*B. henselae* 1:1024 B.quintana 1:512	Normal complement levels, elevated RF, proteinase 3-ANCA (PR3-ANCA) and myeloperoxidase ANCA	Not applicable	Not applicable	Ampicillin-sulbactam IV 7 weeks and Gentamicin 2 weeks (culture negative endocarditis), followed by 2 weeks Ceftriaxone IV, Gentamicin IV and Doxycycline. Self discharged before more antimicrobials given. Declined valve surgery.	Creatinine, CRP and PR3-ANCA decreased, skin purpura disappeared, 2 months post DC echo with warts remarkably regressed
[10]	60 yo Male	Yes	None	Mitral	Subarachnoid hemorrhage/mycotic aneurysm	4 set prior to antimicro-bials Negative	*B. henselae* 1:1024	None	Valve PCR testing positive *B. henselae*	Not applicable	2 weeks of Gentamicin plus Doxycycline, followed by 4 weeks of Doxycycline. Post-antimicrobial mitral valve replacement for continued deterioration and continued evidence of mycotic aneurysm. Retreated with 2 weeks of Gentamicin plus Doxycycline and 4 weeks of Doxycycline	Not reported
[24]	66 yo female	Yes	Yes, bioprosthetic aortic valve	Negative TEE, but fulfilled all five condi-tions for modified Duke minor criteria	Crescentic glomerulonephritis, Right central retinal artery occlusion, leukopenia & thrombocytopenia	Multiple sets negative	*B. henselae* 1:1600	MultipleANA 1:320, Positive RF, c-ANCA positive	Bartonella PCR testing on kidney biopsy tissue negative	Not applicable	2 weeks of Gentamicin and 4 months of Doxycycline, until titer decreased to 1:400. Almost started on Rituximab, in addition to steroids prior to return of positive *B. henselae* titer	
[25]	Male	Yes						None				

(*continued on next page*)

Table 2 (*continued*)

	Age/Gender	Contact with cats	Pre-existing heart valve disorder	Valve involved	Other manifestations	Blood cultures	Bartonella serology by IFA	Autoimmune workup	Other testing (Karius, etc)	16 S Ribosomal DNA amplification and sequencing	Treatment: surgical, antimicrobials	Outcome
			Yes, bicuspid aortic valve with two separate aortic valve replacements	Bioprosthetic aortic valve	Acute renal failure, two aneurysmal hemorrhagic stroke, eventually heart failure	Several negative	*B. henselae* IgG 1: > / = 1024, IgM 1:20		DNA PCR positive initially, negative subsequently.	Valve tissue cultures negative. Pathology report with healing vegetation on healing bioprosthetic valve, occasionally weakly gram-negative bacilli	IV Ceftriaxone, Doxycycline and Rifampin for 6 weeks, followed by 2 weeks of Rifampin and 6 weeks of Doxycycline. Returned with HF, had heart transplant, then 6 months of Doxycycline post transplant.	One year post transplant no evidence of infection relapse
[16]	Male	Unknown	Bicuspid aortic valve	Aortic valve	Splenic infarct, immune complex glomerulonephritis	Negative	None	CRP 4.9, ESR 25, C3 94 mg/dL, C4 23 mg/dL, ANCA negative, MPO-ANCA negative, PR3-ANCA positive	Valve path with necrosis, neutrophils, *B. henselae* on tissue culture and specialized stains	Not done	Valve replacement, 6 weeks of Doxycycline and Rifampin	Improved urinalysis and creatinine post treatment. ESR and CRP normalized
[26]	Male	Yes	No	Aortic	Lymph nodes, lungs, bone, SQ, epididymis	Negative despite 3 weeks incubation	Not reported	None	PCR amplification of short fragment (151 bp) of the pap31 gene using specific primers (higher sensitivity than 16 S rDNA)	Not applicable	Levofloxacin, Azithromycin, doxycycline, and Gentamicin (no duration)	Gradual improvement
[27]	Male	Yes	Bioprosthetic pulmonic valve and right ventricle to pulmonic artery conduit repair	Bioprosthetic pulmonic valve	Focal segmental proliferative glomerulonephritis and incomplete crescent formation	Negative	*B. henselae* IgG > / =1:1024,- IgM > / = 1:20	Elevated ESR/CRP, C3 normal, C4 marginal low, ANCA positive	Unknown	Unknown	Prednisone and 6 weeks IV Doxycycline	He admitted to not completing course after readmit 1 year later for AKI, persistently elevate IgG levels, with chronic end-stage glomerulonephritis and HF. Re-do pulmonic valve, repeat course of Doxycycline
[28]	Male	Yes	Unknown	Aortic	Janeway lesion	Negative	*B. henselae* IgG 1:16,384 *B. quintana* 1:16,384	None	Not done	Aortic valve tissue positive for B quintana	Aortic Valve replacement Ceftriaxone+doxycycline +azithromycin (added for salvage therapy). Gentamicin not used: CKD stage 3	Severe myocardial dysfunction
[28]	Male	Yes	Unknown	Mitral	CVA	Negative	*B. henselae* IgG 1:32,768 B.quintana 1:16,384	C3: 81 mg/dL, C4 4.2 mg/dL, RF 102 UI/mL	Not done	Not applicable	Doxycycline+Rifampin +Gentamicin	Deceased from massive transformation of brain infarct
[4]	Male	Yes				Negative		cANCA 1:256		Not applicable		

(*continued on next page*)

Table 2 (*continued*)

	Age/Gender	Contact with cats	Pre-existing heart valve disorder	Valve involved	Other manifestations	Blood cultures	Bartonella serology by IFA	Autoimmune workup	Other testing (Karius, etc)	16 S Ribosomal DNA amplification and sequencing	Treatment: surgical, antimicrobials	Outcome
			Yes, Rheumatic heart disease and bioprosthetic AV		Postinfectious glomerulopathy, AKI on presentation		*B. henselae* IgG 1:32,768 *B. quintana* IgG 1:512 C.burnetti phase II IgG 1:256		Not applicable		2 weeks of PO Doxycycline, IV Ceftriaxone and IV Gentamicin, followed by additional 4 weeks of IV Ceftriaxone plus PO Doxycycline, then indefinite suppression with PO Doxycycline	one year post diagnosis no further CV complications/ need for surgery, repeat *B. henselae* IgG titer 1:2048
[29]	Male	No-Dogs	No	Aortic	Daily fever, splenomegaly	Negative	*B. henselae* > 1:64 B.quintana > 1:64	Not done	Nested PCR targeting fstZ region and molecular testing targeting Bartonella spp DNA: both noting *B. henselae*	Not applicable	Gentamicin+Unasyn, followed by Doxycycline 200 mg daily to complete 6 weeks	Followed 5 years later with no complications from endocardial vegetation
[30]	Male	Yes	yes, bicuspid aortic valve	Aortic valve	No	Negative	Not available in UK	None mentioned	No	Aortic valve +	Aortic valve replaced. Amoxicillin/Gentamicin, followed by Doxycycline x 6 weeks and Gentamicin x 14days	Full recovery, no long term follow up
[31]	Female	Yes	Bioprosthetic pulmonary valve and pacemaker	Negative TEE	Acute diffuse proliferative glomerulonephritis	Negative	*B. henselae* IgG 1:1024, IgM 1:64, *B. quintana* negative	Decreased C3/C4, initial ANCA inconclusive, positive in speckles pattern, PR3 Ab positive	Not applicable	Not applicable	15 weeks of Doxycycline and Rifampin	Bartonella PCR undetectable, Serum creatinine declined over 3 months
[32]	male	Yes	Aortic graft, mechanical aortic valve and MV annuloplasty ring	Aortic graft and Aortic valve	Splenomegaly, Elevated CRP, thrombocytopenia, fevers, and acute kidney injury	Negative	Not checked	None mentioned	Serum PCR +, confirmed with Western Blot	Not checked	No surgery. Ceftriaxone/ Doxycycline, followed by Ceftriaxone for 8 weeks and Gentamicin for 4 weeks then life-long doxycycline	Full recovery
[33]	Male	Yes	Bicuspid aortic valve	Aortic valve	Brain, kidney and spleen infarcts	Negative	*B. henselae* IgG > 2048, IgM 20	Elevated ESR, CRP, RF, cANCA and anti-PR3 antibody. C4 low, C3 normal, Lupus anticoagulant detected	Not done	16S rRNA positive, Histopath of valve with poorly staining coccobacilli, Aortic valve culture on special agar plates positive for *B. henselae*, Aortic valve grindings analyzed for rpoBgene + *B. henselae*	Initially treated with aspirin and unfractionated heparin; steroids were planned but not started. IV Ceftriaxone 6 weeks, IV Gentamicin 2 weeks and Doxycycline PO 3 months	Full recover at 7 months, inflammatory marker normalized
Patel et al., 2021 – current case	65 Male	Yes	Mitral	Bicuspid aortic valve, repair in childhood	Crescentic glomerulonephritis, respiratory failure	Negative	*B. henselae* > 1:1024, *B. quintana* 1:512	ANA/ANCA negative	Karius, positive for *B. henselae*	Not performed	Mitral valve replacement. Rifampin + doxycycline x 17 days then gentamicin + doxycycline x 14 days, plan for doxycycline x 6 weeks thereafter	Deceased on hospital day 34 following PEA arrest

complex diseases such as postinfectious GN, lupus nephritis, IgA nephropathy and vasculitis, as well as anti-glomerular basement membrane disease and antineutrophil cytoplasmic antibody (ANCA) vasculitis [15]. Interestingly, there is evidence of ANCA positivity in serum for many *Bartonella* endocarditis patients, with one review demonstrating 77% of cases with these findings [16]. Furthermore, a 2014 case report and literature review of *Bartonella* endocarditis cases reported that 50% of the eight reviewed cases were c-ANCA positive [4]. The correlation between CGN and *Bartonella* endocarditis may be one where, in settings of unexplained renal failure and concordant findings on biopsy, the diagnosis of *Bartonella* should be considered.

To further assess this correlation, we reviewed 17 case reports between 2010 and 2020 (Table 2). These cases were selected based on diagnosis of infectious glomerulonephritis via renal biopsy and/or an extensive autoimmune work up. In 7 of the 17 cases the patient underwent renal biopsy, revealing features characteristic of crescentic glomerulonephritis, with treatment of Bartonella resulting in restoration of renal function. Concurrent infectious and auto-immune work up was completed in 10 cases given symptoms and negative blood cultures.

In axenic media, *Bartonella* species appear to be susceptible to many antimicrobials, including penicillin, cephalosporins, fluoroquinolones, macrolides and aminoglycosides, but the correlation between in vivo and in vitro is lacking [17]. Gentamicin is the aminoglycoside that appears to be most studied [18]. There appear to be limited or no prospective studies to support treatment guidelines for endocarditis, and most recommendations are largely based on retrospective, observational data. Many experts recommend dual therapy for effective treatment, at least in the initial 2 weeks [18]. The AHA (2005 edition) recommends using doxycycline for 6 weeks after valve surgery or 12 weeks total if the valve is retained and gentamicin for at least 14 days. Alternatives to doxycycline are macrolides with recommendation for 12 weeks minimum with valve surgery and 6 months without surgery. Valve replacement seems to be central to appropriate therapy, having occurred in 80% of past cases [17]. If gentamicin cannot be used, notably in settings where renal function is a concern, the alternative is rifampin for at least 14 days. Gentamicin is chosen because aminoglycosides are bactericidal, and doxycycline has been shown to penetrate erythrocytes. The combination works well to eradicate the bacteria in different niches within the host [18,19]. In a retrospective study of 101 patients, at least 14 days of aminoglycosides (in combination with another antimicrobial) demonstrated higher rates of recovery as compared to non-aminoglycoside monotherapy [20]. The question remains whether bactericidal activity is required for clearance of the organism. Some data shows *Bartonella* residing within erythrocytes may afford protection from gentamicin, hence the recommendation to use more than one agent [19]. Interestingly, there is in vitro data to support the use of azithromycin/ciprofloxacin and rifampin/ciprofloxacin combinations to completely eradicate biofilms after 6 days and kill stationary phase *Bartonella* after day 1 of exposure [21]. The total duration of antimicrobial treatment is not clearly defined, leaving room for future guidelines to assist with clarification.

Conclusion

Bartonella endocarditis remains difficult to identify and manage. Several concurrent presenting symptoms may lead the clinician towards this diagnosis, including renal failure with an auto-immune-like component. NGS may have an up-and-coming role in both diagnosis and treatment. Treatment remains largely surgical, with improved outcomes seen with the use of combination antimicrobial therapy.

Ethical approval

Not applicable-no studies conducted on the patient.

Consent

Not applicable-no studies conducted on the patient/no patient identifying information used in the case report.

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Author contribution

Roshni Patel, Kansas Koran and Amanda Schnee contributed composition and construction of the work. Mark Call assisted with critical edits.

Disclosure

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