

Recurrent Bacterial Endocarditis Complicated by Acute Kidney Injury

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Renal dysfunction in the setting of acute bacterial endocarditis is relatively common, occurring in up to one third of affected patients.¹ A careful examination of the history, laboratory studies, and urine microscopy may elicit the etiology of renal dysfunction; however, renal biopsy may be indicated in some cases. Potential causes of renal dysfunction in endocarditis include glomerulonephritis, septic emboli, renal infarction, ischemic renal injury associated with acute tubular necrosis (ATN), or iatrogenic causes such as antibiotic-induced acute interstitial nephritis (AIN) or nephrotoxicity from aminoglycosides. Clinical management of renal dysfunction is dependent on the underlying cause. This article presents the case of a man with bacterial endocarditis who developed acute kidney injury after receiving aminoglycosides.

CASE PRESENTATION

Initial Presentation and History

A 39-year-old man with a history of recurrent bacterial endocarditis presented to the emergency department with fevers, weakness, and increased lethargy. The patient was uncooperative, and his wife provided most of the initial history. She reported that he last used intravenous (IV) drugs during the week prior to admission and had fevers with chills for the past 3 to 4 days. The patient noted periods of diplopia and nausea and vomiting over the past few days.

Past medical history was remarkable for several episodes of bacterial endocarditis, IV drug abuse, hepatitis C, and a seizure disorder thought to be related to alcohol abuse. He had approximately 10 bouts of bacterial endocarditis with different organisms occurring over 7 years, each time treated with prolonged courses of antibiotics. Bacteriologic cure was evident, but the patient subsequently relapsed as a result of his continued IV drug abuse. Previous organisms causing bacterial endocarditis in the patient included methicillin-susceptible *Staphylococcus aureus* (MSSA) and various species of *Streptococcus* in the α -hemolytic streptococcal group, including *Streptococcus mitis*, *Streptococcus para-*

sanguis, *Streptococcus sanguis*, *Streptococcus gordonii*, and *Streptococcus salivarius*.

Three months prior to presentation, the patient was hospitalized in the intensive care unit for alcohol withdrawal complicated by grand mal seizures, acute respiratory distress syndrome, gastrointestinal bleeding of unidentified source, and MSSA endocarditis that resulted in a tracheotomy and placement of a percutaneous gastrostomy tube, which was removed prior to the patient signing out against medical advice. Several past episodes of bacterial endocarditis had been complicated by acute kidney injury attributed to ATN. He had evidence of central nervous embolic disease on neuroimaging, with several previous cerebrovascular accidents that did not result in residual neurologic deficits. He currently had no complaints of gross hematuria, dysuria, or frothy urine.

The patient denied dental pain, history of recent dental procedures, and oral contamination of his injection needles. He was not taking any of his prescribed outpatient medications, and he had no known drug allergies. Family history was remarkable for a seizure disorder in his mother but no known renal disease. Social history revealed active tobacco, alcohol, and substance abuse with IV heroin and cocaine.

Physical Examination

The patient's temperature was 100.5°F, heart rate was 107 bpm, blood pressure was 130/75 mm Hg, respiratory rate was 12 breaths/min, and oxygen saturation was 98% on room air. In general, the patient was somnolent but agitated when awakened. Examination of the face and head was normal, and the sclera were anicteric. Oropharyngeal and dental examination was unremarkable. Fundoscopic examination did not reveal any

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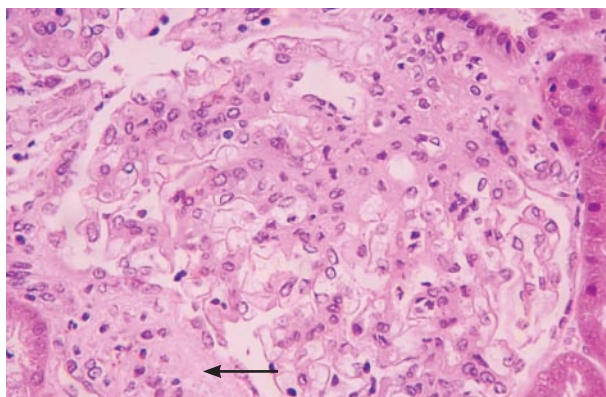


Figure. Light microscopy view of kidney specimen showing an abnormal glomerulus that is hypercellular with endothelial swelling and many inflammatory cells. Note the adhesion or a small crescent at the lower left (arrow), which is consistent with proliferative glomerulonephritis.

evidence of Roth's spots. He had no palpable lymphadenopathy. Cardiovascular examination was remarkable for a 3/6 holosystolic murmur best heard at the apex and radiating to the axilla, which had been noted in previous examinations. Lungs were clear to auscultation bilaterally, and the abdomen was benign with no hepatosplenomegaly. Extremity examination revealed no pitting edema, Janeway's lesions, Osler's nodes, or splinter hemorrhages. Dermatologic examination revealed a few petechiae over the patient's scalp, which his wife first noted a few days ago. Although initially limited due to the patient's somnolence, neurologic examination was nonfocal and revealed that he was oriented to time, place, and person.

Laboratory and Imaging Studies

Initial laboratory testing was normal, including blood urea nitrogen (10 mg/dL), serum creatinine (0.9 mg/dL), white blood cell (WBC) count (9600 cells/ μ L), hemoglobin (12.6 g/dL), hematocrit (36.7%), and platelet count (240,000 cells/ μ L). A routine urinalysis obtained shortly after admission revealed 60 red blood cells (RBCs) and 8 WBCs per high-power field and 200 mg/dL of protein. A urine spot protein/creatinine ratio was 1.75, suggesting approximately 2 g of proteinuria daily. Urine microscopy revealed many dysmorphic RBCs with a few WBCs, granular casts, and RBC casts. Magnetic resonance imaging of the head revealed evidence of old cerebrovascular accidents as well as interval development of a new acute infarct in the left paramedian pontine area, which was thought to represent an embolic infarct. HIV enzyme-linked immunosorbent assay was negative. Transthoracic echocardiogram re-

vealed thickened mitral valve leaflets with a new small mobile structure attached to the posterior mitral leaflet, severe mitral regurgitation, and normal systolic function; the remaining valves were unremarkable.

Treatment and Outcome

The patient was diagnosed with acute endocarditis and initially treated with vancomycin 1 g every 12 hours, penicillin 4 g every 4 hours, and gentamicin 60 mg (1 mg/kg) every 8 hours based on his normal renal function. Blood cultures returned positive for viridans streptococci, and the antibiotics were consolidated to penicillin and gentamicin after susceptibilities returned. On hospital day 8, the patient developed nonoliguric acute kidney injury with a subsequent peak serum creatinine level of 1.7 mg/dL (normal, 0.6–1.2 mg/dL) and a blood urea nitrogen level of 17 mg/dL (normal, 8–23 mg/dL). He had no hypotension during the hospitalization and was essentially asymptomatic during this period. Initially, gentamicin levels were therapeutic, with a trough of 1.3 μ g/mL and a peak of 2.7 μ g/mL, but levels subsequently became supratherapeutic 7 days into his antibiotic course just prior to the development of renal failure, with a trough of 2.5 μ g/mL and a peak of 4.3 μ g/mL. Repeat urine microscopy showed interval development of muddy brown casts in addition to dysmorphic RBCs and RBC casts. Complement levels, specifically C3 and C4, were normal, but total hemolytic complement (CH50) was low. Rheumatoid factor and serum cryoglobulins were positive. The gentamicin dose was adjusted to account for the decreased glomerular filtration rate, but the renal failure did not resolve, and a renal biopsy was performed on hospital day 12.

Light microscopy evaluation of the kidney specimen revealed a diffuse proliferative glomerulonephritis with 20% crescent formation in the glomeruli and evidence of acute tubular damage with regenerative activity (**Figure**). An immunofluorescence study revealed focal and segmental glomerular deposition of IgG along the glomeruli. Other antisera, including IgA, IgM, and C4, were negative. Electron microscopy revealed a few scattered electron-dense deposits occurring along the capillary walls. The biopsy results suggested glomerulonephritis consistent with a peri-infectious immune complex etiology and evidence of ATN. Gentamicin was discontinued, and the patient was treated with a 42-day course of ceftriaxone that was well tolerated. The patient's renal function improved with antibiotic therapy alone. The serum creatinine level at discharge was 0.9 mg/dL, and urinalysis prior to discharge revealed 10 RBCs per high-power field and 50 mg/dL of protein. Although

the patient did not follow-up in the nephrology clinic as planned, he presented to the emergency department 1 year after discharge from the hospital with continued active IV drug and alcohol abuse, and his serum creatinine level remained stable at 0.8 mg/dL; a urinalysis at the time revealed no RBCs and no protein.

RENAL DYSFUNCTION DUE TO BACTERIAL ENDOCARDITIS

Renal dysfunction occurs in approximately one third of patients with bacterial endocarditis and is associated with an increased risk of mortality. In 1 retrospective review, the presence of acute kidney injury increased the odds of death fivefold.¹ Renal dysfunction in bacterial endocarditis classically is due to an immune complex glomerulonephritis. Glomerulonephritis occurred in approximately 20% to 26% of patients with endocarditis-related renal dysfunction in pathology studies.^{2,3} Septic emboli, renal infarction, and ischemic renal injury resulting in ATN either as an effect of septic physiology or acute valvular compromise are also common. Iatrogenic causes of renal dysfunction in endocarditis include antibiotic-induced AIN or nephrotoxicity from aminoglycosides.² In a retrospective study of renal biopsy and necropsy results of 62 patients with confirmed infective endocarditis, 31% of patients had renal infarcts, 26% had acute glomerulonephritis, 11% had AIN, and 10% had renal cortical necrosis.²

Aminoglycoside-Induced Acute Tubular Necrosis

Aminoglycosides are recommended as first-line agents to be used in combination with other antibiotics in the treatment of many bacteriologic causes of endocarditis.⁴ ATN is a well-known side effect of aminoglycoside therapy, occurring in 5% to 30% of patients.^{5,6} The timing of renal failure development after initiation of aminoglycoside therapy is important for diagnosing aminoglycoside-induced ATN; renal failure usually occurs after at least 5 days of therapy and becomes increasingly prevalent with prolonged therapy.⁶ Aminoglycoside-induced ATN is clinically characterized by a slow rise in serum creatinine and nonoliguric renal failure and may be associated with significant proximal tubular dysfunction, at times causing associated proteinuria, glucosuria,⁷ hypocalcemia,⁸ hypomagnesemia, metabolic alkalosis, and hypokalemia.⁹ Risk factors for the development of aminoglycoside-induced ATN in addition to duration of therapy include concomitant use of vancomycin^{10,11} or angiotensin-receptor blockers, anemia, hypotension, advanced age, frequent aminoglycoside dosing, and a diagnosis of diabetes mellitus or liver disease.¹²⁻¹⁴ Once-daily consolidated dosing of aminoglycosides has been shown to decrease the risk

of nephrotoxicity¹⁰ but has not been shown to be efficacious in the treatment of endocarditis; therefore, once-daily dosing is not recommended over standard frequent dosing in patients with endocarditis. Although concomitant use of vancomycin has been associated with an increased risk of nephrotoxicity,^{10,11} penicillins may have some renoprotective effects when used in conjunction with aminoglycosides.¹⁵ One study found that prolonged use of vancomycin alone and gentamicin alone was associated with a 5% and 11% incidence of acute kidney injury, respectively, whereas the combination of vancomycin and gentamicin was associated with a 22% incidence of acute kidney injury.¹¹ It should be noted that patients who require vancomycin for treatment may have more chronic illnesses or more frequent hospitalizations that place them at increased risk for infection with a resistant organism.¹⁶ Interestingly, 1 prospective study showed that patients with methicillin-resistant *Staphylococcus aureus* are more likely to develop acute kidney injury and have persistent bacteremia than patients with endocarditis due to MSSA.¹⁷

Endocarditis-Related Glomerulonephritis

Renal dysfunction caused by diffuse glomerulonephritis is associated with failure of antimicrobial therapy and failure to recover renal function. Patients who do not develop significant renal dysfunction from endocarditis-related glomerulonephritis appear to have a good renal prognosis with antibiotic therapy alone.^{3,18} Patients may develop endocarditis-related glomerulonephritis despite appropriate antibiotic therapy, and the development of renal failure may be delayed until several days after antibiotic therapy is initiated.¹⁸ The presence of proteinuria and hematuria, depressed levels of serum complement, and circulating rheumatoid factor are suggestive of endocarditis-related glomerulonephritis. Because the underlying endocarditis should be treated first before considering immunosuppressive measures to treat glomerulonephritis, many clinicians choose to forego renal biopsy; however, in some clinical circumstances (eg, renal failure despite appropriate antibiotic therapy, when other etiologies of renal failure are possible), renal biopsy results can guide management decisions.

The most appropriate treatment for patients with renal dysfunction secondary to endocarditis-related glomerulonephritis is unknown. Most cases of endocarditis-related glomerulonephritis appear to resolve spontaneously with appropriate antimicrobial treatment of the underlying infection.^{3,18} Several case reports have described successful recovery of renal function with the use of corticosteroids and plasmapheresis after renal function did not recover with antimicrobial

therapy.¹⁹⁻²⁶ The rationale for using such therapy is that endocarditis-related glomerulonephritis is thought to be mediated by an immune mechanism. This immune mechanism is associated with high levels of circulating immune complexes, hypocomplementemia, and immune complex and complement deposition in the glomerular basement membrane.^{27,28} Steroid therapy generally has only been added after prolonged antibiotic therapy, and the doses of steroids vary from oral prednisone (60-80 mg/day) to pulse IV methylprednisone (500 mg for 3 days followed by 100 mg/day).²²

In patients with hepatitis C and IV drug abuse, other potential causes of chronic glomerular disorders can be considered. The most common glomerular lesion associated with chronic hepatitis C infection is membranoproliferative glomerulonephritis;²⁹ other glomerular disorders associated with hepatitis C include membranous glomerulonephritis, IgA nephropathy, and focal segmental glomerulosclerosis.³⁰ In the case patient, these diagnoses were considered, and a renal biopsy was helpful in ruling them out.

SUMMARY

In this patient, the differential diagnosis of the cause of his renal failure included endocarditis-related glomerulonephritis, ATN secondary to gentamicin therapy, a glomerular disorder associated with his chronic hepatitis C virus infection or IV drug abuse, or AIN secondary to penicillin therapy. The renal biopsy was helpful in confirming the diagnosis of glomerulonephritis, particularly because the abnormal urinary findings did not occur until several days into his antibiotic therapy. The identification of ATN on this patient's renal biopsy prompted the discontinuation of aminoglycosides to prevent further problems with his renal function. Once susceptibilities and mean inhibitory concentrations were obtained, antibiotic therapy was safely switched to ceftriaxone alone. If this patient's renal function continued to worsen despite treatment with appropriate antibiotics, steroid or plasmapheresis therapy may have been considered. **HP**

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