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Case report

A rare cause of healthcare-associated infective endocarditis: *Enterobacter cloacae*

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A B S T R A C T

We report a case of infective endocarditis secondary to healthcare-associated bloodstream infection caused by an uncommon etiologic agent, multidrug-resistant *Enterobacter cloacae*. The patient was treated with a combination of antimicrobial therapy and surgery, but could not be saved. With this case, we discuss the prevalence, risk factors, treatment options, and outcomes of the rarely encountered *Enterobacter cloacae*-associated infective endocarditis.

Introduction

In patients with end-stage renal failure, infective endocarditis (IE) is a serious infectious disease with a high risk of mortality. Gram-positive bacteria are usually the cause, although a gram-negative organism is occasionally identified as the etiologic agent [1]. In a study reviewing 2761 patients with definitive IE diagnoses, gram-negative bacteria other than HACEK organisms (*Haemophilus* spp., *Aggregatibacter* spp., *Cardiobacterium* spp., *Eikenella corrodens*, and *Kingella* spp.) were reported in only 1.8% of the cases. Among these, *E. coli* and *Pseudomonas* were the two most frequently isolated microorganisms, whereas *Enterobacter* was detected in only 2 patients. The authors determined that endovascular devices and healthcare-associated infections were important risk factors for non-HACEK gram-negative IE [2].

In this report, we present a rare case of *Enterobacter* endocarditis following vascular catheter-related bacteremia in a patient undergoing hemodialysis for chronic kidney disease. We will highlight the prevalence, risk factors, treatment options, and outcomes of *Enterobacter*-associated IE through this case.

Case

A 54-year-old female presented to the hospital with a 10-day history of fever over 38 °C. She had been diagnosed with chronic kidney disease 8 years earlier and she had undergone hemodialysis with an arteriovenous (AV) fistula for 6 years, and for the last 2 years she had hemodialysis 3 times a week through a permanent central venous catheter. Under follow-up at another center, she developed catheter-related bacteremia approximately 1 year earlier and cultures yielded *E. cloacae* sensitive to third generation cephalosporins. During this period, her catheter was not removed and she received multiple courses of antimicrobial therapy. Most recently, she was prescribed amoxicillin-clavulanate 1000 mg daily for 5 days at another medical center for her current complaints. There was no other peripheral and catheter blood culture result until her admission to the infectious diseases unit of our hospital due to the persistent fever.

At time of admission, the patient exhibited fever (38.5 °C), hypotension (80/50 mmHg) and tachycardia (115 beats/min). An area of redness less than 2 cm was observed on the skin at the insertion site of the permanent central catheter in the right subclavian vein. Other than bilateral renal atrophy, findings on anterior-posterior chest x-ray and abdominal ultrasonography were normal. Laboratory findings were hemoglobin = 9.46 g/dL; white blood cell (WBC) count = 21.97 × 10^3/μL; platelet count = 137 × 10^3/μL; C-reactive protein = 11.3 mg/dL; serum creatinine = 8.57 mg/dL; blood urea nitrogen = 46.6 mg/dL; and serum albumin = 2.47 g/dL. Suspecting central venous catheter-related bloodstream infection, 2 sets of catheter and peripheral blood samples were obtained for culture, and treatment with daptomycin 8 mg/kg intravenously (IV) once every 48 h and piperacillin-tazobactam 2.25 g IV 4 times daily was initiated.

Within the first 24 h, the right subclavian venous catheter was removed and a catheter was inserted in the left jugular to continue hemodialysis. *E. cloacae* was detected in all peripheral and catheter blood sample cultures. Antibiotic susceptibility testing showed the strain was resistant to piperacillin-tazobactam and third-generation cephalosporins but susceptible to carbapenems and aminoglycosides. On day 3 of therapy, piperacillin-tazobactam and daptomycin were discontinued and replaced with meropenem 500 mg IV once daily. On day 6, the

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patient's fever had not responded to treatment. Laboratory findings were hemoglobin = 8.92 g/dL; WBC count = 18.09 × 10^3/μL; platelet count = 214 × 10^3/μL; CRP = 14.5 mg/dL; serum creatinine = 5.24 mg/dL; blood urea nitrogen = 40.3 mg/dL; and serum albumin = 2.66 g/dL.

The lack of response raised suspicion of IE. Transthoracic echocardiography showed a 10 × 2 mm vegetation on the tricuspid valve and subsequent transesophageal echocardiography revealed 8 × 8 mm vegetation on the lateral tricuspid valve leaflet. Gentamicin 3 mg/kg IV once every 48 h was added to the antibacterial therapy. On day 13 of hospitalization, laboratory findings were hemoglobin = 8.42 g/dL; WBC count = 10.003 × 10^3/μL; platelet count = 298 × 10^3/μL; and CRP = 15.2 mg/dL. Follow-up transesophageal echocardiography showed the vegetation on the tricuspid valve had grown to 15 × 10 mm in size. Tigecycline was added to the antibacterial therapy with a 100 mg loading dose (IV) followed by 50 mg IV twice daily. As the vegetation continued to grow and the infection could not be controlled in 13 days despite appropriate antibacterial therapy, surgery was recommended. Under cardiopulmonary bypass with bicaval cannulation, the vegetative mass was scraped from the posterior leaflet of the tricuspid valve. The tricuspid valve was repaired using DeVaga annuloplasty. In addition, an atrial septal defect was closed primarily with sutures. *E. cloacae* was also detected in culture of the excised vegetation. The patient was followed postoperatively in the intensive care unit and died on the second postoperative day due to septic shock associated with *E. cloacae* bacteremia.

Discussion

IE is characterized by vegetations which form as a result of inflammation due to bacterial or fungal infection of the endocardium and/or heart valves [3]. IE occurs most frequently in the aortic valve, followed by the mitral valve, and both the aortic and mitral valves; tricuspid valve involvement is rare [4]. Reports in the literature indicate it is more common among the elderly and the male sex, and has an annual incidence of 2.4–11.6 per 100,000 [5–8].

Enterobacter is a rare etiology of endocarditis. In a meta-analysis of 2761 confirmed endocarditis cases, only 2 were due to *Enterobacter*. This meta-analysis determined that more than half of all patients with non-HACEK gram-negative bacterial endocarditis had healthcare-related infections and most had endovascular devices such as prosthetic valves, or permanent cardiac pacemakers or defibrillators [2]. In another study analyzing 363 cases in order to identify risk factors in the IE population, chronic hemodialysis was reported to be the most common risk factor in IE populations and was associated with higher 30-day mortality [9]. Vascular access was determined to be the main risk factor in patients with chronic kidney disease. Furthermore, the risk of bacteremia was reported to be higher in hemodialysis performed through a permanent or temporary vascular catheter compared to arteriovenous graft or fistula [10]. Our patient, who underwent hemodialysis for eight years and developed endocarditis secondary to healthcare-associated bloodstream infection related to a persistent vascular catheter, had all of these risk factors.

The increasing antibacterial resistance of gram-negative bacteria is concerning. It has been reported that 25% of bacteremic episodes in hemodialysis patients were caused by gram-negative pathogens and a significant proportion of them were sensitive only to colistin [10]. *Enterobacter* spp. are naturally resistant to aminopenicillins, cefazolin, and cefoxitin due to the production of chromosomal AmpC β-lactamases [11]. The use of third-generation cephalosporin induces expression of AmpC-type β-lactamases in *Enterobacter* strains and can cause permanent resistance. It has been reported that in bacteremic patients, the use of third-generation cephalosporins may result in selection of AmpC-overproducing mutants, leading to the emergence of resistant strains and, as a consequence, higher mortality [12]. It has also been reported that non-HACEK gram-negative bacterial endocarditis has a high mortality risk. A case series reviewing *Enterobacter* endocarditis reported a 37.7% mortality rate [13]. Our patient was previously followed for a catheter-related bloodstream infection associated with a sensitive *Enterobacter* strain. Her catheter was not removed and her antimicrobial use during this period likely resulted in the emergence of a resistant mutant *Enterobacter* strain. We believe that this situation, which increases mortality, was also a major factor in the death of our patient.

Although successful results have been reported with monotherapy in the treatment of *Enterobacter*-associated IE, the European Society of Cardiology guidelines recommend early surgical intervention and at least 6 weeks of β-lactam and aminoglycoside treatment, with the addition of quinolones or cotrimoxazole when advised by specialists [13,14]. In addition, in an animal model of *Enterobacter aerogenes* endocarditis, the addition of gentamicin to aztreonam and cefoperazone treatment promoted faster and more comprehensive reduction of vegetation titers, thus demonstrating the superiority of combination therapy [15]. Studies of *Enterobacter* endocarditis cases followed at different centers report that including surgery in the therapeutic approach lowers mortality rates. However, authors also warned against making definitive conclusions due to variables such as the choice of surgical procedure, antibacterial use, comorbid conditions, and medical care [2,13]. The British Society of Antimicrobial Chemotherapy guidelines recommend immediate surgery in cases with fever and positive blood cultures persisting for ≥10 days despite the initiation of appropriate antibacterial therapy, as in our case [16]. The primary surgical treatment options are valve replacement for aortic valve involvement and repair in cases of mitral and tricuspid valve involvement [17].

Our patient was treated with appropriate combined antimicrobial therapy for approximately ten days and underwent surgical tricuspid valve repair. The procedure was high-risk due to the patient's clinical status and comorbidities, and the patient did not survive. Removal of vegetation by percutaneous access has been presented as an alternative for the treatment of right-sided endocarditis in patients with hemodynamic instability [18,19]. This procedure was reported to reduce bacterial load and enable hemodynamic stabilization until a definitive surgery [18]. However, we did not utilize this procedure due to the lack of sufficient evidence in the literature and the presence of tricuspid valve insufficiency in our case.

Conclusion

Healthcare encounters and history of antibacterial use are risk factors for antimicrobial resistance in gram-negative microorganisms. Hemodialysis patients comprise an important risk group for non-HACEK gram-negative bacterial endocarditis due to vascular access and frequent healthcare-associated infections. We believe combined antibacterial therapy is necessary in hemodialysis patients with life-threatening infections such as endocarditis.

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