

Culture-Negative Infective Endocarditis Caused by *Aerococcus urinae*

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Aerococcus urinae is a rarely reported pathogen that often causes mild urinary tract infection (UTI), although serious complications such as endocarditis and septicemia have also been described. The organism may easily be missed or misidentified when using commercial detection systems. *A. urinae* is resistant to sulfonamides and, therefore, a typical treatment for UTI may be inappropriate. To date, 14 cases of *A. urinae* infective endocarditis (IE) have been reported, most of which were elderly males with predisposing conditions to UTI. Of these

Infective endocarditis (IE) is a serious cardiac disease that is associated with a high mortality rate. The diagnosis of IE is based on the fulfillment of Dukes' criteria, notably positive blood cultures for a specific pathogen and abnormal echocardiography (1). Unfortunately, conventional microbiological methods yield a significant proportion (up to 31%) of negative results in cases of clinically suspected IE. This may be due to previous antibiotic therapy or infections with fastidious, slow-growing, or difficult-to-culture pathogens (2). More recently, molecular approaches have helped to overcome some of these limitations. Specifically, the amplification of bacterial 16S rRNA genes from samples of cardiac tissue, followed by sequencing of the polymerase chain reaction (PCR) product and homology analysis, has been reported as a promising method of identifying the causative bacterial microorganisms in IE patients (3,4).

Herein is reported a case of blood culture-negative IE caused by *Aerococcus urinae*, a rarely identified human pathogen. *A. urinae* is a Gram-positive coccus that

grows in pairs and clusters as alpha-hemolytic colonies on blood agar. Most infections are mild, but serious sequelae such as endocarditis and septicemia can occur. To date, a total of 14 cases of *A. urinae*-mediated IE has been reported, including eight fatalities.

patients, eight died and 50% of survivors had severe neurological problems. The case is reported of blood culture-negative IE in a 69-year-old male. The patient recovered fully after undergoing aortic valve replacement and receiving a nine-day course of intravenous ceftriaxone, followed by peroral cefuroxime for the next 11 weeks. The causative agent was identified from the excised valve by bacterial broad-range PCR and direct sequencing of the 16S rRNA gene.

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Case report

A 69-year-old male was admitted to the regional hospital with dehydration, preceded by high fever and diarrhea. Seventeen days before admission, the patient had been prescribed clarithromycin to treat fever, cough and bloody rhinitis, but had stopped taking the antibiotic because his fever and other symptoms had subsided. However, 10 days before hospital admission the fever had returned, accompanied by chills, diarrhea, and frequent urinary voiding. These symptoms disappeared, without treatment, after three days.

On admission, the patient was afebrile, the pulse was 120/min, and blood pressure 120/80 mmHg. On physical examination the lungs were clear, but an aortic diastolic murmur was heard. Other than an enlarged prostate gland, no other pathological findings were noted. The patient's past medical history included surgical treatment for a urinary bladder papillocarcinoma 15 years ago, cholecystectomy one year ago, obstructive pyelonephritis and benign prostatic hyperplasia diagnosed three years ago, and diabetes type II which was being controlled by dietary means. The laboratory

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investigations provided the following data: hematocrit 31.5%, erythrocyte sedimentation rate 105 mm/h, C-reactive protein 66 mg/l, and serum creatinine 138.5 mmol/l; all liver function tests were normal. A urine sediment analysis showed sporadic leukocytes, and both urine and blood cultures were repeatedly negative. Abdominal ultrasonography demonstrated normal kidneys but chronic hepatopathy and an enlarged prostate gland; cystoscopy was normal. No foci of infection were identified by urology, otorhinolaryngology and dental examinations and work-ups. Chest X-radiography disclosed a dilated heart. Transthoracic echocardiography showed grade 3 aortic regurgitation, while transesophageal echocardiography (TEE) revealed the presence of a 3.8×4.0 mm vegetation which was connected with a right coronary aortic valve leaflet. Upon this finding, the patient was transferred to the Centre for Cardiovascular Surgery and Transplantation, in Brno.

During a previous one-month period of hospitalization the patient had initially received ceftriaxone and ciprofloxacin, but at the time of transfer he was receiving amoxicillin clavulanate (2×375 mg daily). Repeated TEE confirmed hemodynamically significant aortic regurgitation and the presence of a 10 mm-long pendulous vegetation. Based on the modified Duke's criteria (1), the findings were concluded to be consistent with a diagnosis of possible IE, and the patient was scheduled for surgical treatment. In addition, coronary angiography revealed significant stenoses (>80%) on the circumflex and right coronary arteries. A double aortocoronary bypass was performed on both affected arteries, combined with removal of the insufficient aortic valve (including vegetation) and its replacement with a biological valve (St. Jude Medical Epic 25, model EL-25A).

A molecular examination by broad-range PCR of the excised valve tissue revealed *A. urinae* with sequence homology 99% (GenBank, Accession Number AY422713), despite the culture remaining negative. Based on these findings, which were available within 24 h, cefuroxime (3×1.5 g, i.v.) given immediately after surgery was switched to ceftriaxone (2×2 g, i.v.). The choice of ceftriaxone was based on a previously reported excellent experience of treatment of IE caused by *A. urinae* (5). Echocardiography performed on postoperative day 7 showed normal function of the aortic valve, and on day 10 the patient was discharged in stable condition, with the ceftriaxone being replaced with peroral cefuroxime (2×500 mg daily) for the next 11 weeks. The patient was followed up as an outpatient and remains without any sequelae one year after surgery.

Discussion

Aerococcus urinae is an uncommon pathogen that may be associated with urinary tract infections (UTIs), soft tissue infections, bacteremia, sepsis and, rarely, IE (6-8). The laboratory diagnosis of *A. urinae* can be difficult, because it is a microaerophilic, catalase-negative coccus that may be mistaken for alpha-hemolytic streptococci or enterococci. Most patients infected with *A. urinae* are elderly males with predisposing conditions who present initially with UTIs.

To date, a total of 14 cases of *A. urinae* endocarditis has been reported (5,9,10,11). The identification of the bacterial pathogen responsible for IE in the present patient relied on molecular detection because blood and urine cultures were performed only after the start of antibiotic treatment, and were negative; bacterial culture of the excised valve tissue also remained negative. The present patient is the second case in which *A. urinae* was identified by PCR amplification of the bacterial 16S rRNA gene; this technique utilized broad-range PCR followed by direct sequencing and sequence homology analysis (4).

Typical predisposing factors for *A. urinae* IE are male gender, age >65 years, and pre-existing urinary tract pathologies (5), all of which were present in this case. Systemic comorbidities, such as diabetes mellitus, malignancy or ischemic heart disease, were reported in five of the 14 *A. urinae* IE patients (5,9,10,11), although this high number may be due to a greater frequency of these disorders among the elderly population. Indeed, the present patient suffered from diabetes, had significant stenoses on two coronary arteries, and a history of urinary bladder papillocarcinoma.

A. urinae IE has a very poor prognosis, with eight of the 14 reported cases proving fatal and three of six survivors having neurologic sequelae. Currently, there are no guidelines for the choice of antibiotic treatment (due to too-few cases), although beta-lactams alone or in combination with aminoglycosides have been suggested for prolonged six-week intravenous treatment (5). Ebnöther et al. (5) also reported the successful treatment and full recovery of one patient by surgical valve replacement followed by six-week therapy with ceftriaxone and netilmicin. The present patient underwent surgical aortic valve replacement concurrently with bypass of the two coronary arteries that were found to be stenosed. Surgery, in combination with intravenous ceftriaxone followed by peroral cefuroxime for 11 weeks, resulted in a full recovery.

In conclusion, IE caused by *A. urinae* is a life-threatening condition with high mortality or consequent morbidity. The disease is most likely under-diagnosed due to difficulties encountered when culturing and identi-

fying this microorganism. *A. urinae* should be considered as a pathogenic agent of IE in all patients with the above-described predisposing conditions. Broad-range PCR, followed by direct sequencing, might represent a valuable diagnostic approach for this infection, especially in culture-negative cases.

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