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Case Report

Microbiology Section

Infective Endocarditis Caused by Multi-drug Resistant Corynebacterium Species: A Case Report

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ABSTRACT

Corynebacteria species are anaerobic, facultative, non-sporing, gram-positive bacilli that can cause infective endocarditis. In recent years, non-diphtherial *Corynebacterium* (diphtheroids) has increasingly been recognised as a cause of both localised and systemic infections. Determining the exact species of *Corynebacteria* is challenging due to their similar characteristics. Infective Endocarditis (IE) caused by *Corynebacteria* species is uncommon because positive blood cultures might be considered contaminants, leading to missed diagnoses. However, they can indeed cause IE, which is a severe condition. Antibiotic resistance among *Corynebacteria* species is common and has been increasing, making treatment challenging. In-vitro resistance to vancomycin cannot be detected reliably. Literature on IE caused by *Corynebacteria* species is limited, and more comprehensive information is needed. In cases of IE caused by *Corynebacteria* species, prosthetic valves are mainly affected, especially in elderly patients, and surgery is often required. Within the *Corynebacterium* genus, *Corynebacterium striatum* is a major causative agent of IE. Although *Corynebacteria* species in blood cultures are often considered contaminants from skin flora, they can also cause invasive infections such as sepsis and IE. The present case report describes the isolation of *Corynebacteria* species from the blood specimen of a 50-year-old male who presented with fever, headache, decreased appetite, and fatigue.

Keywords: Antibiotic resistance, Blood culture, Valve replacement, Vancomycin

CASE REPORT

A 50-year-old male patient, with an unknown case of IE, presented to the emergency department with symptoms including fever, frontal headache, loss of appetite, and fatigue. The patient had a high-grade, intermittent fever, chills without rigors, and a compressing frontal headache without associated aura, vomiting, etc. He was a known case of systemic hypertension for the past 10 years and was on medications for it. Additionally, he had hypertrophic cardiomyopathy with a bicuspid aortic valve that caused moderate aortic stenosis and regurgitation. He had undergone aortic valve replacement five years ago and was currently on warfarin therapy.

During the examination, the patient was conscious, oriented, and febrile, with a temperature of 40°C. There were no signs of pallor, jaundice, cyanosis, clubbing, or pretibial oedema. His pulse rate was 92 bpm, blood pressure was 90/80 mmHg, and oxygen saturation was 98% on room air. On chest auscultation, a loud P2 was heard in the aortic area, along with a prosthetic click. Respiratory, abdominal, and central nervous system examinations were normal. Blood tests, such as a complete blood count, showed raised leukocytosis (26,500/mm^3), while renal and liver function parameters and other tests were Within Normal Limits (WNL). Tests for urine cultures, malaria antigen, dengue NS1/IgM, scrub IgM, and Widal test were negative. Transthoracic echocardiography showed a normal study with no vegetations and normally functioning valve. Blood and urine samples sent for culture showed no growth.

The patient was started on empirical intravenous injection (i.v.) ceftriaxone 2 gm for seven days and oral azithromycin 500 mg for three days. However, he continued to have fever spikes after one week of antibiotics. An ultrasound of the abdomen revealed mild splenomegaly, and the patient was then started on i.v. Amikacin 3 mg/kg per 24 hours in three equally divided doses for two weeks. These findings suggest a possible case of IE. Two blood cultures, drawn more than 12 hours apart, were sent and both cultures grew "*Corynebacteria spp*" that were sensitive to penicillin and amikacin. After two weeks of treatment, the patient developed fever again, leading to the suspicion of thrombophlebitis, and a bone marrow sample was sent for culture, which also grew "*Corynebacteria spp*" that were resistant to penicillin but sensitive to vancomycin and amikacin. Therefore, i.v. vancomycin 30 mg/kg/24 h in two equally divided doses and amikacin 3 mg/kg per 24 hours in three equally divided doses were continued for four and two weeks, respectively. Splenomegaly improved, but the patient continued to have fever spikes, leading to suspicion of internal jugular vein thrombophlebitis. Repeat echocardiography showed normal findings.

After six weeks, *Candida spp*. was reported from blood drawn from the i.v. catheter, indicating catheter-related bloodstream infection. The patient was then started on fluconazole. The catheter line tip was removed and sent for culture, which also grew *Candida spp*. After 12 weeks using an automated blood culture system, "*Corynebacteria spp*" grew again, this time showing resistance to vancomycin. The antimicrobial therapy was changed to i.v. linezolid 600 mg twice daily during the hospital stay. The patient showed clinical improvement and was symptomatically better. For further follow-up, the patient was advised to continue taking medications, and there was no recurrence of symptoms or reinfection after a three-month review on an outpatient basis.

DISCUSSION

According to a study by Grenna B et al., the incidence of *Corynebacterium endocarditis* was estimated to be one in a million per year [1]. *Corynebacteria* species cause serious infections in immunocompromised patients with prosthetic devices in place. When patients present with recurrent bacteraemia and an unknown source of infection, it is important to consider the diagnosis of IE [2]. A systematic review by Belmares J et al., concluded that *Corynebacterium endocarditis* mainly affects the left side of the heart and is more commonly seen in males. Adults are at a higher risk than children for nosocomial *Corynebacterium endocarditis*, which can occur due to the presence of prosthetic devices, invasive procedures, and intravascular access [3]. In a study by Muttaiyah S et al., 10 cases of *C. diphtheriae*-IE were found [4].

In this particular case, the patient initially had a febrile illness with a broad differential diagnosis, including enteric fever, scrub typhus, urinary tract infection, meningitis, or a viral disease. The differential diagnosis narrowed down only when the microbiology results showed a positive blood culture. Considering the presence of valve replacement, the source of *Corynebacterium* bacteraemia, and the possibility of IE were taken into account. This case met three minor criteria (predisposition, fever >38°C, microbiologic evidence with positive blood culture) under possible IE, according to the modified Duke's criteria for the diagnosis of IE. Early valve-related IE infections can occur through bacteraemia from the site at the time of insertion or by seeding of bacteria either before or after valve insertion [5]. In this case, the source of the bacteraemia could be an occult source of sepsis that has remained dormant since the valve replacement surgery five years ago.

When blood cultures isolate *Corynebacterium*, it is often mistaken as contamination from normal skin flora rather than as a pathogen causing a true infection. Several cohort studies by Kimura SI et al., Ishiwada N et al., and Yanai M et al., showed that between 44% and 71% of patients with *Corynebacterium* bacteraemia had a true infection [6-8]. Some studies have relied solely on the bacteriological criterion (≥2 positive blood cultures) [6,7], while a few studies have shown that clinical features and the presence of intravascular devices are risk factors for true infection [9,10]. Rasmussen M et al., modified the definitions for true infection caused by "*Corynebacteria spp*" based on three criteria. Two or more blood cultures yielding *Corynebacterium* with signs of infection, such as a temperature ≥38°C, systolic blood pressure <100 mmHg, chills, and leukocytosis, were defined as true infection (criteria 1). Contamination was defined as two or more positive blood cultures with more pathogenic bacteria (criteria 2), and a focal infection where another organism is more likely to be the cause (criteria 3) [11].

The site of infection grew another bacterium or a focal infection such as pneumonia, soft tissue infection, or urinary tract infection, which excluded true infection. If *Corynebacterium* grew from the site of infection or the focal infection was Infective Endocarditis (IE), spondylitis, or arthritis, it was considered a true infection. However, only one blood culture isolated *Corynebacterium*, and the episode had to fulfill all three criteria. In addition, an intravascular device should have been placed for more than 48 hours or *Corynebacterium* had to be isolated from the site of infection to be considered as bacteraemia [11].

Skin commensal bacteria, specifically *Corynebacteria spp*, can cause IE in the presence of artificial valves and/or intracardiac devices. If all blood culture sets of patients grew *Corynebacterium* and they were pre-diagnosed to have IE, it should be considered as the aetiology, and the growth should not be considered as contamination [12].

In the present case, *Corynebacteria spp* grew in all (6/6) of the blood culture samples. There have been some case reports of IE caused by *Corynebacteria spp* resulting in subacute infections, especially in elderly patients with comorbidities, those on immunosuppressive treatment, or with intracardiac devices. Surgery is often required, and the mortality rate is significant. Patients with IE mainly caused by *Corynebacteria spp* (70%) were significantly more likely to have Prosthetic Valve Endocarditis (PVE) compared to other pathogens (14%-39%). Surgery was performed in 50% of the patients with PVE caused by *Corynebacterium*, which was significantly higher than other pathogens. PVE due to *Corynebacteria spp* prolonged the median duration from the onset of disease to hospital stay [13].

Multidrug-Resistant (MDR) *Corynebacterium* infections have occurred in immunocompromised patients with intracardiac devices during prolonged hospital stays and exposure to broad-spectrum antibiotics [12]. The patient in this case was immunocompromised and had undergone valve replacement surgery. Additionally, they had a history of hospital stays and antibiotic use. Increased antibiotic resistance of *Corynebacteria spp* to beta-lactams and rifampicin has been observed. Although antibiotic resistance to *Corynebacteria spp* is common, resistance to vancomycin could not be detected in-vitro [13].

The microorganism in this case was determined to be resistant to vancomycin, which is currently the drug of choice for empirical treatment of *Corynebacterium* endocarditis. Linezolid, available in both oral and intravenous formulations, is an alternative treatment for MDR *Corynebacterium* infections. However, a strain resistant to linezolid has never been reported. In the literature review, only one case was treated with oral linezolid after four weeks of vancomycin. The therapy was continued for an additional 28 days [14].

In the present case of endocarditis due to *Corynebacteria spp*, it was managed with intravenous linezolid after four weeks of vancomycin, resulting in a good outcome and no reinfection after three months of follow-up.

CONCLUSION(S)

Corynebacteria spp. is an uncommon cause of artificial valve endocarditis, which is a serious disease. It should not be reported as a contaminant when grown in a blood culture, especially in immunocompromised patients and/or those with prosthetic devices. The presented case is a rare instance of valve replacement-related IE caused by *Corynebacteria spp*. This bacterium is becoming increasingly resistant, and numerous antibiotics have been reported, making treatment more challenging. Using oral antibiotics instead of parenteral therapy could be a key strategy to decrease antimicrobial resistance. The use of oral linezolid, in particular, may lead to a shorter hospital stay, which could help reduce the presence of resistant strains in the hospital environment and minimise transmission to non-infected patients. Once the patient reaches a stable condition, the efficacy and safety of administering oral antibiotics may be similar to vancomycin therapy. However, new trials and prospective studies are required to confirm this therapeutic strategy.

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