

Case Report

Late-onset prosthetic valve endocarditis caused by nontoxigenic *Corynebacterium diphtheriae*

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Abstract

In developed countries, *Corynebacterium diphtheriae* infection is rare due to efficient immunization programs. However, cases of nontoxigenic strains of *C. diphtheriae* infections, including endocarditis, have been reported recently. Although the incidence remains low, these infections are associated with high morbidity and mortality. This report describes the first and atypical case of bacteremia and endocarditis caused by nontoxigenic *C. diphtheriae* var. *gravis* after introduction of immunization in the Kingdom of Saudi Arabia (KSA).

Key words: nontoxigenic *Corynebacterium diphtheriae*; endocarditis; complication.

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Introduction

Over 120 species of the genus *Corynebacterium* are known [1]. *Corynebacterium* species, or "diphtheroids", are aerobic, pleomorphic Gram-positive bacilli that are often considered to be non-pathogenic normal flora of the skin and mucous membranes. Although frequently isolated in cultures, they are commonly ignored and assumed to be contaminants [2]. *C. diphtheriae* is the most important infective agent of this genus and must be distinguished from other *Corynebacterium* species. After widespread immunization with diphtheria toxoid, diphtheria became increasingly rare [3]. More recently, nontoxigenic strains of *C. diphtheriae* (NTCD) have been recognized to cause disease in many countries with high diphtheria vaccination coverage [4-9]. The spectrum of NTCD diseases ranges from cutaneous lesions and pharyngitis to severe invasive disease with bacteremia, endocarditis, septic arthritis, and splenic abscesses [6-12]. This report describes the first-ever case of a patient with infective endocarditis (IE) due to NTCD, complicated by a cerebral infarction and septic emboli in the Kingdom of Saudi Arabia (KSA) after the introduction of vaccination.

Case report

In February 2014, a 14-year-old boy was referred to the emergency and accident department at King Khalid University Hospital with a clinical diagnosis of endocarditis complicated by a cerebrovascular accident with slurred speech, right-sided deviation of mouth, and left-sided weakness for one day. At the time admission, the patient admitted that he had been suffering from fever with chills for the last two weeks. The patient was being treated with oral bisoprolol 2.5 mg, furosemide 40 mg, lisinopril 2.5 mg, and aspirin 81 mg once daily since July 2013 following mitral and aortic tissue valve replacement due to rheumatic heart disease (RHD). The patient was on intramuscular benzathine penicillin, 1.2 million units monthly, for prophylaxis of RHD until July 2013, which was discontinued after valve replacement. His immunization was up to date, including the diphtheria toxoid vaccine.

On examination, he was conscious, oriented, and alert. He was febrile (38.9°C), and his other vital signs were normal. Neurological examination revealed right-sided tongue deviation, left upper- and lower-limb grade 3/5 weakness with normal power in his right side and normal tone in both sides. He had positive plantar reflexes in his left side. Sensation and cerebellar system examinations were not performed because of a lack of cooperation. Apart from a systolic

murmur with normal first and second heart sounds, the cardiovascular system examination was unremarkable. No abnormality was detected on examination of other systems.

The initial laboratory investigations showed leukocytosis (42,000 white blood cells per microliter) with 85% neutrophils; erythrocyte sedimentation rate was 62 mm/h (normal, 0–20 mm/h), and his C-reactive protein (CRP) level was 190 mg/L (normal, 0–8 mg/L). The activated partial thromboplastin time (APTT) was 40.3 seconds, and the international normalized ratio (INR) was 1.4. In total, two sets of blood cultures were sent to the microbiology laboratory.

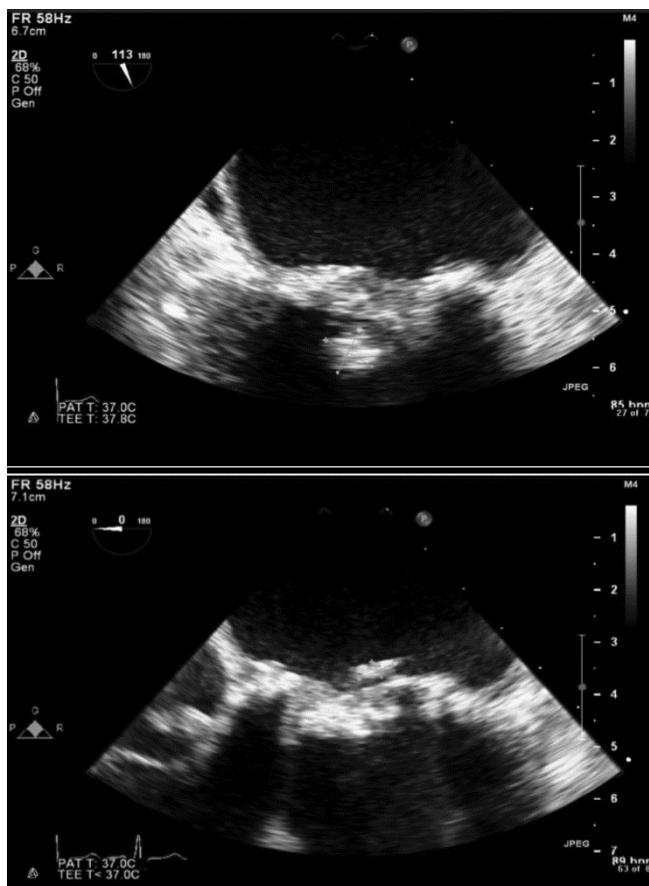
A transthoracic echocardiography (TTE) showed thickened mitral bioprosthetic valve leaflets with restricted motion (Figure 1). Two masses were observed; the larger of the two measured approximately 1.5 cm and exhibited free mobility. The appearance of the mass was consistent with bioprosthetic valve vegetations consistent with the diagnosis of IE. The transprosthetic mitral and aortic bioprosthetic gradients were remarkably high. A plain computerized tomography (CT) brain scan revealed right frontal-temporal-parietal acute infraction in the distribution area of the middle cerebral artery. The definitive diagnosis of IE was made based on clinical and radiological findings according to the Duke criteria.

An empirical treatment with 2 g ceftriaxone intravenously (IV) daily was initiated and later on,

1,250 mg vancomycin IV every 12 hours and 80 mg gentamycin IV every 8 hours were also added after recommendations by the infectious disease physician. Dosages of vancomycin and gentamicin were adjusted according to their serum levels. Because of the mitral valve vegetations and the possibility of thrombo-embolic phenomenon, anticoagulation therapy with heparin and warfarin was started. Physiotherapy was also initiated.

On the day following admission, both aerobic and anaerobic blood culture bottles revealed club-shaped Gram-positive rods suggestive of diphtheroid bacteria. Further incubation of the cultures on blood agar yielded small Gram-positive non-hemolytic rods that were catalase positive and devoid of tumbling mobility, thus excluding *Erysipelothrix rhusiopathiae* and *Listeria monocytogenes* [13]. These bacteria were preliminarily identified as *Corynebacterium* species and were susceptible to penicillin and vancomycin using the minimal inhibitory concentration (MIC) method (E-test) (MIC = 0.19 µg/mL and 0.75 µg/mL,

Figure 1: Echocardiograph showing two vegetations on the prosthetic mitral valve



respectively) and were intermediate to ceftriaxone (MIC = 1.5 µg/mL). This isolate was subsequently identified as *C. diphtheriae* by an API coryne strip test (product no. 20900; bioMérieux, Marcy l’Etoile, France). For further identification, the isolate was sent to a reference laboratory (Bioscientia Laboratory, Ingelheim, Germany), and it was finally confirmed to be nontoxigenic *C. diphtheriae* var. *gravis* by real-time polymerase chain reaction (PCR) for diphtheria toxin gene detection.

On the third day of hospital admission, based on antimicrobial susceptibility testing, the patient was switched from ceftriaxone and vancomycin to 4 million units of penicillin G IV every 4 hours and 100 mg gentamicin IV every 8 hours. Subsequently, all of the blood cultures collected four days after initiation of antibiotic therapy were negative.

On the fifth day following admission, the patient suffered from partial thrombosis of the right iliac artery and a splenic infraction; he recovered well after emergency right iliac artery embolectomy. During the third week following admission, he again underwent

an emergency left tibial artery embolectomy and had a complete recovery. Following these thrombo-embolic episodes and persistent vegetations on the thickened prosthetic heart valves detected by repeat transesophageal echocardiography (TEE), he underwent emergency cardiac surgery for aortic and mitral valve replacement. Peroperatively, the patient was found to have pericardial adhesions, bioprosthesis with vegetations, periannular abscess, and atrioventricular groove adhesions. Surgical debridement of the infected tissue and abscess drainage were performed. Both aortic and mitral valves along with swabs from the abscess were sent to the microbiology laboratory. Direct sample examinations, Gram stain, and cultures were negative. Postoperatively, the patient was treated with 1 gm vancomycin IV every 12 hours and 4 million units penicillin G IV every 4 hours for 6 weeks, and gentamicin 100 mg every 8 hours for 2 weeks. Anticoagulant treatment was initiated to maintain APTT of 60–70.5 seconds for heparin and INR of 2.5–2.8 for warfarin. The TEE two weeks after cardiac surgery revealed no abnormality, and since the patient was hemodynamically stable, he was eventually allowed to go home with 4 mg warfarin orally daily. Echocardiography performed two weeks after the completion of antibiotic therapy did not indicate any vegetation.

Discussion

The most important pathogen of *Corynebacterium* species remains *C. diphtheriae*, the causative agent of diphtheria, which has declined significantly after the implementation of universal vaccination targeting diphtheria toxin (DT) [3]. As a consequence of the decreased prevalence of diphtheria, there has been a recent surge in NTCD infections, especially invasive diseases including IE, in countries such as Brazil [14], France [8,15], India [11], Poland [9], the United Kingdom [6], the United States [4,12], and New Zealand [7].

In the KSA, diphtheria, pertussis, and tetanus (DPT) immunization coverage was 100% among one- and six-year-old children in 2002 [16]. Following this, a number of studies performed in the KSA failed to report the presence of *C. diphtheriae* in blood culture specimens of patients suffering from various diseases, including IE [17-20]. This appears to be the first-ever report of bacteremia and endocarditis due to NTCD var. *gravis* in the KSA after implementation of the DPT vaccination. Although NTCD was isolated from a blood specimen of a patient with IE in 1987, the

organism was not biotyped [21]. In countries where anti-diphtheria vaccination is being regularly implemented, the spectrum of diseases caused by *C. diphtheriae* has been altered [6-9,12], resulting in increased prevalence of NTCD infections, which can occur in DPT-immunized populations [6,8]. The causative agent in this patient was NTCD biotype *gravis*, similar to the organism isolated from invasive infections in Poland [9,15], the United States [4,12], and New Zealand [7]. In contrast to these observations, biotype *mitis* dominated among the invasive isolates in France [15], indicating a regional variation in the distribution of biotypes. The age of this patient was in agreement with previous reports, where 80% patients suffering from NTCD endocarditis were under 30 years of age [6-8,11,22]. Several predisposing factors for NTCD infections have been identified; these include intravenous drug use, low socioeconomic conditions, alcoholism, homelessness, diabetes mellitus, hepatic cirrhosis, and dental caries in addition to immune-compromised status [6,7,12,22]. However, there is enough evidence suggesting that NTCD infections can occur in persons with no identifiable predisposing factors or concomitant diseases [7]. The presence of a prosthetic heart valve appears to be the most likely predisposition in this case, as a number of studies have reported that patients with valve replacement, preexisting cardiac disease, or abnormalities are at a higher risk for having *Corynebacterium* IE [4,7,11,22].

NTCD endocarditis has been described as an aggressive and destructive disease with frequent thrombo-embolic complications [10,11], which were also observed in this patient. Systemic embolization rates in IE range from 22% to 50%, and neurological complications develop in 20% to 40% of patients [23]. It has been documented that 70% of IE survivors who experience a cardio-embolic stroke achieve full neurological recovery after cardiac surgery [24].

C. diphtheriae is generally sensitive to antibiotics that act on the cell wall such as penicillin, cephalosporins, vancomycin, and teicoplanin. Penicillin and gentamicin are known to act synergistically, and the NTCD endocarditis treatment with both the antibiotics may have contributed to the favorable outcome in this study. However, multidrug-resistant *C. diphtheriae* strains have also been isolated [14], and NTCD strains resistant to penicillin and third-generation cephalosporins have been reported in patients with IE [10]. Since the mortality rate attributed to *Corynebacterium* endocarditis is high (43.4%) [22], effective and prompt patient-specific

management, including clinical expertise, advanced cardiac imaging, and antibiotic therapy may also have contributed to better outcomes.

Conclusions

The findings of this case report highlight the seriousness of NTCD endocarditis and its associated complications. In a clinical setting, detection of *Corynebacterium* isolates in blood culture specimens, usually considered to be a contaminant, should not be ignored, particularly in the presence of predisposing factors. Large retrospective studies are recommended to determine the prevalence of NTCD in the KSA.

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