Case Report

The resurgence of *Corynebacterium diphtheriae*: A rare case of infective endocarditis

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ABSTRACT

Corynebacterium species or "diphtheroids" are often considered as non-pathogenic components of the normal skin flora when isolated from blood culture. Invasive diseases like infective endocarditis with *Corynebacterium diphtheriae* are an unusual presentation. We report the case of a 34-year-old man with a medical history of prosthetic valve replacement 12 years back who presented with acute visual loss both eyes and high-grade fever. Echocardiography revealed small particles in the left ventricular outflow tract and the left ventricle probably small detached vegetations. Blood cultures were positive for non-toxigenic *C. diphtheriae.* The patient was diagnosed as prosthetic valve endocarditis caused by non-toxigenic *C. diphtheriae* considering the whole clinical picture, including the patient's medical history, physical examination, and blood cultures.

Key words: *Corynebacterium diphtheriae*, Infective endocarditis, Non-toxigenic

Corynebacterium diphtheriae is well known as an agent of localized respiratory tract disease potentially complicated by systemic effects of exotoxin. The non-toxigenic strains can produce atypical manifestations of the disease as they are able to cause diseases such as mild diphtheria-like pharyngitis, cutaneous infections, septic arthritis, abscesses, septicemia, and infective endocarditis (IE) [1]. IE is a grave disease with a high incidence of complications and adverse events. IE caused due to the non-toxigenic strain of *C. diphtheriae* is uncommon. However, there have been increasing numbers of reports of IE being caused by this organism [2]. The current vaccine against diphtheria contains the toxoid, so it protects only against the toxigenicity but not the invasiveness of *C. diphtheriae.*[1] Most of the patients with *C. diphtheria* endocarditis have underlying cardiac diseases, especially prosthetic heart valves [3]. Pathogenic mechanisms of non-toxigenic *C. diphtheriae* is not well known, and a possible mechanism may be related to an increased ability to adhere to vascular endothelium. It is a universally fatal disease if left untreated with nearly 100% mortality.

CASE REPORT

A 34-year-old prosthetic valve *in situ* male patient who underwent double valve replacement surgery in 2005 presented to our hospital with a 1-week history of high-grade fever with rigor and chills. He woke up 1 day noticing that the entire visual field (both eyes) was obscured. This prompted him to come to the emergency department. No other non-visual neurologic symptoms were present. He was a chronic alcoholic and was on oral anticoagulants.

On general examination, he was conscious and alert. His temperature was 100.5°F, blood pressure 140/80 mmHg, and pulse rate 80/min. Ophthalmic examination revealed only light perception with both eyes and apparently normal fundus.

Investigations revealed that the total leukocyte count was elevated with neutrophil predominance, and erythrocyte sedimentation rate was also elevated. To rule out the acute cerebrovascular accident, plain axial computed tomogram head was done, which could not detect any intracranial pathology. Echocardiography showed normally functioning valves and small particles in the left ventricular outflow tract and the left ventricle.

Suspecting prosthetic valve endocarditis (PVE) for the patient, three blood culture samples were taken and sent to our laboratory. Two samples were taken on the 2nd day of admission and the third sample on the following day after starting the empirical antibiotics. The patient's vision got restored on the 2nd day of admission to the hospital without any interventions.

The blood culture samples were incubated in an automated BacT/ALERT (bioMerieux) blood culture system. After 24 h of incubation, the two samples, which were taken on the 2nd day, flagged positive and Gram staining showed Gram-positive bacilli

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with palisade arrangement. Blood agar showed small white, opaque, and non-hemolytic colonies. Gram staining of the colonies showed Gram-positive coryneform bacteria (Fig. 1a). Metachromatic granules were demonstrated by Albert's staining technique (Fig. 1b). Species identification was done by the Vitek 2 system as *C. diphtheriae* (Bionumber 6361000410005 with 98% probability). The isolate was sent to the State Public Health and Clinical Laboratory, Trivandrum, where the strain was demonstrated to be non-toxigenic with the Elek's immunodiffusion assay (Fig. 2).

He was started on intravenous ceftriaxone and gentamicin initially before receiving the culture results. Due to non-subsiding fever and worsening of renal parameters, both these antibiotics were stopped after 2 weeks and then started on intravenous vancomycin and oral rifampicin. Repeat blood culture done was sterile after 3 weeks of treatment, and the patient was symptomatically better. As the patient's bystanders were planning to continue their treatment in their previous institution where the patient had undergone valve replacement surgery, he was discharged at request after 4 weeks of antibiotic therapy in our institution. He was subsequently lost to follow-up.

DISCUSSION

IE is an infection of the cardiac endothelium. It is a grave disease with a high incidence of complications and adverse events. The

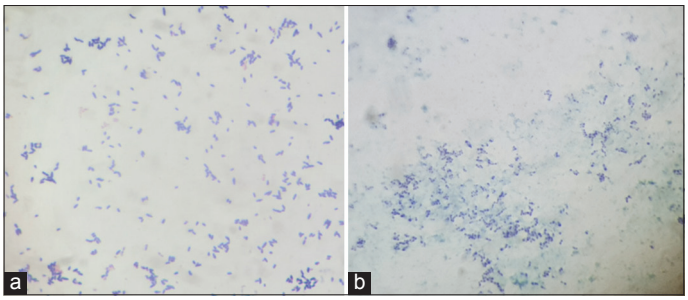

Figure 1: (a) Gram staining of the isolate showing Gram-positive bacilli in palisade arrangement; (b) Albert's staining of the isolate showing the metachromatic granules

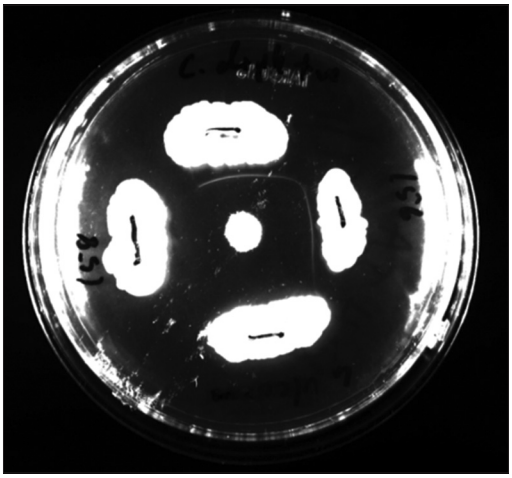

Figure 2: Toxigenicity testing using Eleks gel precipitation test with negative result (Lab ID: 158) along with positive and negative controls

reported incidence of IE is between 1.7 and 6.2/100,000 cases per year, and it has been on the increase and been changing in recent years [4]. The epidemiology, clinical, and microbiologic spectrum of IE is different in the Indian population as compared to the west and usually depends on the type of endocarditis (native valve or prosthetic). In most of the developed countries, native valve endocarditis accounts for 84.5% of cases and PVE accounts for 7–25% of cases of IE [5]. Chronic rheumatic heart disease was found to be the leading cause of chronic valvular disease, comprised 46% of all cases. Common organisms causing IE include *Streptococci, Staphylococci, Enterococci*, and fastidious Gram-negative coccobacilli. Other rare causes are *Mycobacteria, Corynebacteria* spp, *Rickettsia*, *Chlamydia*, and Fungi [6].

The dramatic decrease in the incidence of diphtheria following the introduction of the vaccine has highlighted the emergence of invasive disease. The high rate of immunization with diphtheria toxoid may place selective pressure on the microorganism to develop other pathogenicity factors [1]. This is evidenced by published cases of endocarditis due to non-toxigenic *C. diphtheria* [2,7,8]. *Corynebacteria* have been shown to be responsible for 0.2 to 0.4% of IE cases in the native valve [9]. Non-toxigenic *C. diphtheria* carriage and infections have been most frequently associated with homelessness, low socioeconomic status, crowding, intravenous drug use, and alcoholism; infection has been described in Australian Aboriginals also [10].

The non-toxigenic C. diphtheria probably enters the body following skin, nose, and/or throat colonization or after a percutaneous trauma. Non-toxigenic *C. diphtheriae* can produce atypical manifestations of the disease. The pathogenesis of infection caused by non-toxigenic strains of *C. diphtheriae* is unknown. The organism is capable of tissue invasion and causing fulminant disease and appears to have a predilection for cardiac valvular endothelium and synovium [4]. It is worth to underline that infections connected with *C. diphtheriae* can occur in an immunized population.

Embolic complications in IE can present as neurological abnormalities including stroke or transient ischemic attack, cerebral hemorrhage, mycotic aneurysm, meningitis, cerebral abscess, or encephalopathy, visual disorders, osteomyelitis, arthritis, renal abscess, pulmonary embolism, or glomerulonephritis. Most complications occur early during the course of IE and are a hallmark of the left-sided abnormalities of native or prosthetic valves [11].

The patients can present with sudden onset of visual loss due to metastatic endophthalmitis, panophthalmitis, multiple cerebral infarctions, or ruptured occipital mycotic aneurysm. Emboli can also cause episodes of amaurosis fugax [12]. The transient blindness in this patient may be caused by early cerebritis secondary to vasculitis by the microorganism in the occipital region.

The treatment of IE is cumbersome. *C. diphtheriae* endocarditis has been described as an aggressive disease

requiring urgent surgical intervention, especially in those with prosthetic valves [13]. Most of the cases in the literature were treated conservatively with only 18% requiring surgery and the mortality rate in the reported cases varies between 38% to zero [13]. Decisions regarding the medical treatment of *C. diphtheria*e endocarditis in the past were hampered by the lack of criteria for *C. diphtheriae* susceptibility testing and interpretation. There are no recommended guidelines for the treatment of IE caused by *C. diphtheriae*. Therapy of this endocarditis in the literature is varied, depending on the hospital practice or expert opinions.

The Clinical and Laboratory Standards Institute published interpretive criteria in 2006; a penicillin minimum inhibitory concentration (MIC) of <1 mg/l is considered susceptible [14]. Susceptibility testing of *C. diphtheriae* is not always performed, but studies report a penicillin MIC90 of 0.23 mg/l, well below the cut-off for susceptible [15]. A combination of antibiotics therapy, β-lactam, and aminoglycoside antibiotics is usually described for 4–6 weeks [3]. In our case, blood became sterile after completing 25 days of combined antibiotic therapy without any surgical interventions.

This case was noteworthy for two reasons – one being the unusual presentation of IE with an acute visual field defect secondary to probably cerebritis of the occipital lobe, and the second, being the infective organism. *C. diphtheriae* is often found on the human skin and mucus membranes and in a clinical setting, the detection of Coryneform bacteria in blood cultures is often dismissed as contamination. This case shows that *C. diphtheriae* can cause systemic disease such as IE in susceptible individuals. Species identification of coryneform bacteria, as well as toxin testing if the species proves to be *C. diphtheria,* is important for the therapy of the patient and for the public health officials also.

CONCLUSION

It is very important for all clinicians, as well as microbiologists, to have a high level of suspicion and an open mind regarding uncommon presentations and causes of IE. This would possibly reduce the time wasted before diagnosing the disease, as well as the delay in initiating therapy (antimicrobial or surgical).

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