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Case Report Cardiovascular

Corynebacterium diphtheriae - Uncustomary Avatar in a Patient with Prosthetic Valves at an Unusual Age

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ABSTRACT

Corynebacterium diphtheriae is considered a re-emerging pathogen worldwide. There is a shift in the age in the incidence of diphtheria from children to adolescents and adults reported in India. The majority of the patients with *C. diphtheriae* endocarditis have prosthetic valves and present clinically as an acute fever, septic arthritis, and pharyngitis. In this background, here, we present a case of septic arthritis associated with bacteremia in an adult female with double-valve prosthetic replacement.

Keywords: Adult, *Corynebacterium diphtheria,* Infective endocarditis, Septic arthritis

INTRODUCTION

Although diphtheria has been sometimes overlooked, cases have been documented worldwide within the last several years. In 2015, India reported 2,365 cases of diphtheria which was higher than any other country.[1] Non-toxigenic and toxigenic strains may be present in the nasopharynx, skin, and other sites as asymptomatic carriers.[2] Similar to toxigenic variants, non-toxigenic *Corynebacterium diphtheriae* can cause infection in susceptible individuals with comorbid conditions. Furthermore, non-toxigenic variants can become toxigenic by bacteriophage-mediated lysogenesis. Together, the potential of non-toxigenic strains to obtain the *tox* gene exposes susceptible populations at risk for a diphtheria epidemic.[3] The majority of the patients with *C. diphtheriae* endocarditis have prosthetic valves, underlying heart conditions, or a history of intravenous drug use. Similar to *Staphylococcus aureus, C. diphtheriae* endocarditis presents as an aggressive and destructive illness with a high prevalence of complications, particularly in patients with underlying prosthetic valves.[4] The morphology of toxigenic and non-toxigenic strains is indistinct. Non-toxigenic variants are associated with less disease burden in terms of clinical severity and respiratory and disseminated infection. However, endocarditis, osteomyelitis, and septic arthritis may occur after an infection with non-toxigenic *C. diphtheriae*.[3] In this background, here, we present a case of septic arthritis associated with bacteremia in an adult female with double-valve prosthetic replacement.

CASE REPORT

We reported the case of a 49-year-old female with rheumatic heart disease involving the mitral valve and aortic valve prolapse and chronic atrial fibrillation. She had fever with chills on and off,

giddiness, palpitation, easy fatigability, dyspnea, and swelling over the left knee joint for 3 days. She had a history of a left posterior cruciate ligament avulsion fracture 7 months back, fixed with an external cast. She underwent double-valve replacement 12 years back. On examination, she was afebrile with a pulse rate of 120/min, irregularly irregular with varying volume, a respiratory rate of 28/min, and blood pressure of 110/80 mmHg; SpO_2 was 100%, her throat appeared normal, and cardiovascular examination revealed S1 and S2 sounds, though S1 was variable, while respiratory system assessment indicated normal vesicular breath sounds without any added sounds. The abdomen was soft and no organomegaly was noted.

Laboratory investigations included hemoglobin - 11.7 g% and platelet count - 80,000 lakhs/cumm, and thyroid function test was normal. Echocardiography showed post-aortic and mitral valve replacement with a dilated left atrium and ventricle, moderately severe left ventricular dysfunction, atrial fibrillation, global dyskinesia, aortic prosthetic valve dysfunction, normally functioning mitral valve, no paravalvular leak, and no tricuspid valve regurgitation.

Left knee lateral arthrotomy was done on the next day of admission under spinal anesthesia, and 100 mL pus was aspirated [Figure 1]. Direct Gram stain showed Gram-positive bacilli [Figure 2]. *C. diphtheriae* was isolated [Figure 3], which was sensitive to ciprofloxacin, erythromycin, clindamycin, linezolid, meropenem, and rifampin and resistant to penicillin, tetracycline, cefotaxime, and trimethoprim/sulfamethoxazole. BacT/Alert 3D system aerobic blood culture showed *C. diphtheriae* with the same sensitivity pattern. Bacterial identification by Matrix-assisted laser desorption/ionization- Time of flight (MALDI-TOF) was done with a score value of 1.95.

She was on T. warfarin 7 mg, T. digoxin 0.25 mg, T. Aldactone 25 mg, T. amiodarone, T. esomeprazole, Inj. ceftriaxone, and Inj. linezolid. She developed septic shock with acute renal failure after 2 days. Then, she was given Inj. piperacillin + tazobactam and Inj. vancomycin. Growth on the pus and blood culture were identified only after the 6th day of admission. The patient's condition deteriorated despite appropriate higher antibiotics. The patient succumbed before the institution of the antidiphtheritic serum.

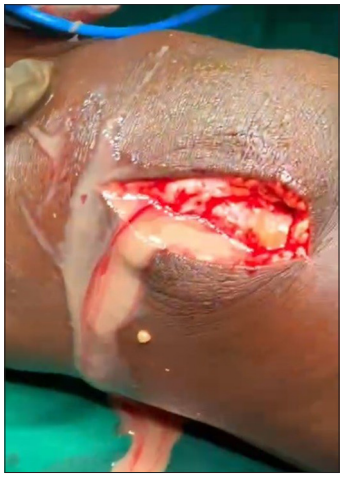

Figure 1: Pus from the left knee joint.

DISCUSSION

At present, *C. diphtheriae* is not only considered a re-emerging pathogen but also remains one of the most significant pathogens worldwide. Originally, it was considered a disease of children; now, there is a shift in the age in the incidence of diphtheria from children to adolescents and adults reported in India.[5]

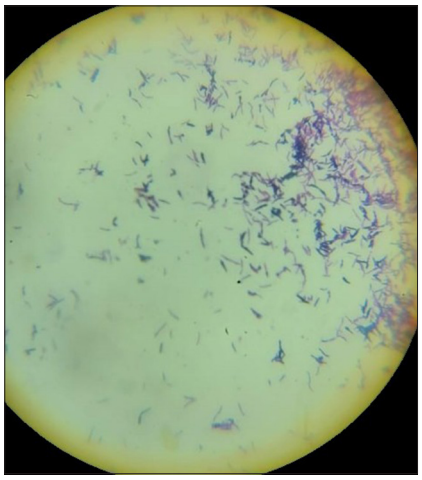

Figure 2: Gram stain showing Gram-positive bacilli. 100× Oil immersion

Figure 3: Culture plate showing *Corynebacterium diphtheriae* colony. Nutrient agar plate showing Corynebacterium diphtheria colonies

Atypical presentation can occur with non-toxigenic strain. The pathogenesis of infection due to non-toxigenic *C. diphtheriae* is inconclusive and needs further studies. They can invade the tissue, cause fulminant infection, and appear to have a predilection for cardiac valvular endothelium and synovium.[6] Studies reported that 80% of endocarditis is due to non-toxigenic *C. diphtheriae*, and typically, previous valvular heart disease is an important risk factor, which is reported in 42–80% of cases, and left-sided endocarditis is more common. Non-toxigenic *C. diphtheriae* endocarditis presents clinically as an acute fever, septic arthritis, and pharyngitis.[7] Endocarditis without vegetations, though rare, can be diagnosed based on the modified Duke's criteria.[8] Joint involvement and bacteremia due to *C. diphtheriae* were also reported.[6] Aspirated pus from joint and blood culture revealed *C. diphtheriae* in this case. The toxigenicity of the strain can be tested *in vitro* by Elek's gel precipitation test, which requires quality control of reagents and a standardized procedure, hence performed only in reference laboratory. Polymerase chain reaction can be performed to demonstrate a subunit of diphtheria toxin, but does not necessarily indicate the toxin production.[9] A non-toxigenic toxin-gene bearing (NTTB) *C. diphtheriae* has been reported in many literatures. These NTTB strains produce challenges in public health management since it is unpredictable when they will revert to full toxicity.[10] The toxigenicity test or *tox* gene demonstration was not performed in this isolate.

Besides toxins, other virulence factors such as iron transport systems and fimbrial proteins are also reported.[1] Some multifunctional proteins such as DIP0733, DIP2093, and CDCE8392-081 are involved in establishing infections in the deeper parts of the body and invasion of the host cells. Astoundingly, the gene *oxyR*, which codes for global oxygen regulator of *C. diphtheriae,* affects the adherence patterns, invasion, intracellular survival in epithelial cells, and arthritogenic potential *C. diphtheriae* in mice. It is clear that *C. diphtheriae* evades the host immune system and persists in the host cells, proliferates, and enters the blood vessels, where they can bind with the erythrocytes (hemagglutination) and spreads throughout the body via the bloodstream. Further, it has a complex cell wall, a mycolic acid layer which is equivalent to outer membrane of Gram-negative bacteria. *C. diphtheriae* HC_{O4} strains show detrimental effect without being toxigenic and induce necrosis and apoptosis of host cells.[11]

Immunization with diphtheria, pertussis and tetanus vaccine (DPT) does not offer protection against the non-toxigenic strain of *C. diphtheriae*. Further, it does not prevent the carriage of *C. diphtheriae*, regardless of toxin production.[12] In highly immunized populations, toxigenic strains virtually disappear, although non-toxigenic strains may continue circulating. Antitoxin is only effective before the toxin reaches the cell; hence, it must be given as soon as possible.[13] The dose of antitoxin is calculated based on the site and severity of infection.[9] Numerous studies have revealed that the protective antibody levels against diphtheria have declined due to aging since the last vaccination, with the antibodies having an estimated half-life of 11 years.[1] Hence, Td is recommended during pregnancy and once in 10 years.[5]

Since the patient did not develop any membrane in her throat, *C. diphtheriae* was not anticipated and antidiphtheritic serum was not given. Atypical presentation due to *C. diphtheriae* should be suspected, especially in patients with prosthetic valves. In addition, it is becoming more common to find *C. diphtheriae* strains that are resistant to antibiotics. Fortunately, the isolates from the pus and blood in this patient were sensitive to most of the routinely used antibiotics. Antibiotic therapy kills the organisms, thus preventing further toxin production, slowing the spread of local infection, and reducing the transmission.[9]

Limitation

The toxigenicity of the isolate was not demonstrated.

CONCLUSION

Unusual presentation due to *C. diphtheriae,* particularly in patients with prosthetic valves, should be kept in mind and antidiphtheritic serum should be given as early as possible if it is a toxigenic strain. Infection can also occur in previously immunized patients. Despite continued global efforts and stable vaccination coverage, diphtheria is not eradicated and remains a problem today. Awareness among clinicians and microbiologists should be increased, and appropriate specimens should be collected, especially in patients with atypical presentation with prosthetic valves.

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