Case Report

Diphtheria resurgence in India: A case study from south Karnataka

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Abstract

Corynebacterium diphtheriae is a gram-positive bacillus with characteristic polar metachromatic granules. It was a significant public health problem, infecting the throat and upper airways and producing a highly potent exotoxin but with the advent of diphtheria vaccine, cases have rapidly decreased. Now over the last decade, the reemergence of this infection has been noted and case reports from India have been documented. India represents 78% of globally reported cases with significant mortality despite national immunization programs in place. This case study indicates the severity of an improperly managed case, the importance of microbiological diagnosis with a special interest in molecular detection, and reinforces a resurgence of diphtheria infection.

Keywords: *Corynebacterium diphtheriae*, diphtheria antitoxin, microbiological diagnosis

Introduction

Diphtheria is caused by gram-positive bacillus known as *Corynebacterium diphtheriae* and was considered a significant public health problem before the advent of universal immunization.[1] However, reports of a possible resurgence are slowly coming to light and primary care physicians along with microbiology laboratories must be able to assist in diagnostics in such cases.[2] The present case suggests that immunization coverage and awareness with appropriate intervention along with laboratory confirmation is lacking. Case study was conducted after obtaining approval from Institutional Ethical Committee and hospital Medical Superintendent.

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Case Report

A 10-year-old male child with unknown immunization history, living away from his parents, was apparently healthy when he presented to a local primary care practitioner with 2 days of high-grade fever, cough with expectoration, and mild swelling of the neck. After initial management for another 5 days, the patient was taken to a secondary care center in view of worsening cough and neck edema. There, the patient was clinically suspected to have diphtheria and crystalline penicillin was administered, following which diphtheria antitoxin was arranged. However, toxigenic symptoms continued and patient was shifted to a tertiary care center. The child was admitted to the pediatric ICU and was started on 60% oxygen via venturi, IV fluids, inotropic support, and antibiotics.

Examination revealed anemia (Hb = 8.8 g/dL), leukocytosis (26.4 $10^3/\mu L$), and mild edema of lower limbs. Tonsils were congested, partially covered with a grayish-white membrane, and severely tender. Upper motor neuron facial nerve palsy and palatopharyngeal incompetence (9th and 10th cranial nerves) were

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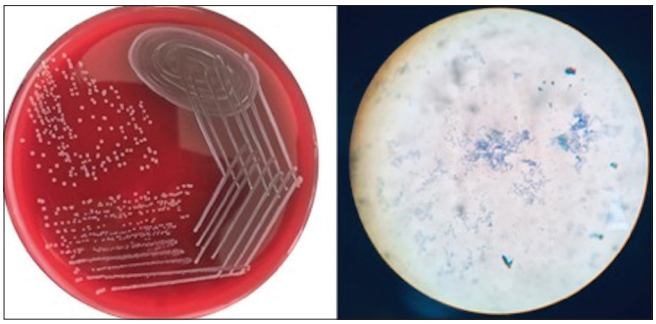

Image 1: *Corynebacterium diphtheriae* on 5% sheep blood agar and Albert's Staining

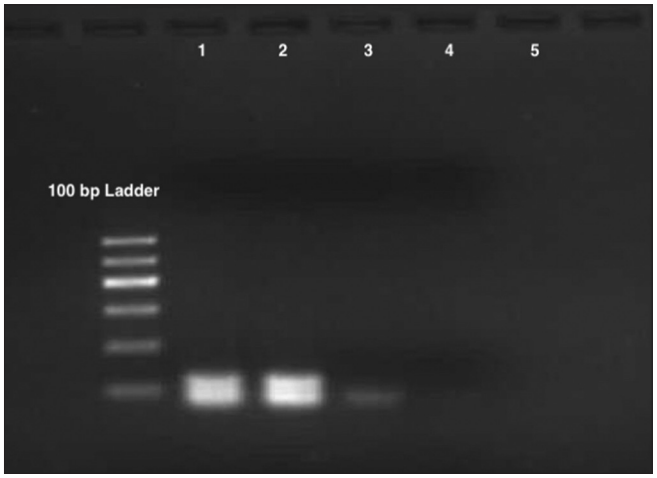

Image 2: *rpoB* and *tox* gene on 1.5% agarose gel. Lane 1: Positive control (rpoB 97bp, tox 117bp), Lane 2: Patient Sample (rpoB 97bp, tox gene 117bp), Lane 3: C. diptheriae strain without tox gene (rpoB 97bp), Lane 4: Negative control

also noted on examination. Mild hepatomegaly and deranged liver functions was also noted (aspartate aminotransferase = 4266 IU/L; alanine aminotransferase = 4398IU/L). Chest radiograph revealed cardiomegaly with pulmonary plethora. In view of significant nephrotic proteinuria (24 h urine protein = 224 mg/m^2/h) and acute kidney injury (serum creatinine = 4.82 mg/dL), renal functions were maintained with diuresis and fluid resuscitation.

On repeat throat swabs at the tertiary center, diphtheria was confirmed by staining and culture [Image 1]. Antimicrobial susceptibility testing (AST) was not performed due to the poor accuracy of automated methods and demanding AST techniques.[3] The strains were tested for *rpoB* and *tox* gene on polymerase chain reaction (PCR) and were found positive [Image 2]. The strains were further sent to a reference laboratory at Christian Medical College, Vellore where it was confirmed. Patient was discharged against medical advice and was found to have expired 2 weeks following discharge.

Discussion

Case reports noting the possible resurgence of diphtheria in India are on the rise, despite multiple national immunization programs in place like "Mission Indradhanush" (MI) and "Intensified Mission Indradhanush" (IMI), which are significant steps toward the hope of diphtheria free nation. India follows the universal immunization program (UIP) recommending 3 doses, 4 weeks apart followed by 2 booster dose schedule; However, average diphtheria-tetanus-pertussis (DPT) vaccine coverage remains at only 84%.[4] Lack of awareness among primary care physicians, delay in clinical suspicion and requests for appropriate investigations are also key factors in mortality associated with such vaccine-preventable diseases. The present case study highlights the possible delays in administration along with limited availability of diphtheria antitoxin (DAT) and the importance of identifying toxigenic *C. diphtheriae* in the laboratory. DAT is not readily available in all health facilities and its manufacture is also at a minimum. It has been suggested that this unavailability may be due to lack of awareness of the reemerging status of the disease and a sense of false security on the immunization coverage as community-based screening of antibody titers against diphtheria has not been evaluated.[5] It is important to understand DAT only neutralizes the circulating toxin and not that bound to tissues; thus, late presentations are closely linked to case fatalities.[6] Furthermore, early diagnosis is paramount in preventing the rapid decline of diphtheria patients, as seen in the present case. Front line physicians and primary care providers are the key players in identifying early manifestations of faucial diphtheria, bacteremia, and toxemia, as initial penicillin therapy can halt disease progression.

Laboratory support for vaccine-preventable diseases can significantly improve outcomes of such cases and provide real-time information on the occurrence of diphtheria, as requisitions for DAT alongside laboratory confirmation can assist prompt response.[7] Recent alterations in clinical and laboratory standards institute (CLSI) AST breakpoints for penicillin susceptible *C. diphtheriae* may be alarming for both microbiologists and clinicians alike, as certain strains which were considered penicillin susceptible before would now be considered penicillin intermediate.[8] Moreover, lack of disc diffusion standards and difficulty of broth dilution methods limit availability for *C. diphtheriae* AST in laboratories across India. Therefore, molecular tests detecting *rpoB* and *tox* gene should be considered for implementation in endemic/high-risk areas to decrease response time for DAT administration.[9] *RpoB* primer pairs: forward 5'-CGT TCG CAA AGA TTA CGG AAC CA-3' and reverse 5'-CAC TCA GGC GTA CCA ATC AAC-3'; with 105bp product and *tox* gene - primer pairs: forward 5'-CTT TTC TTC GTA CCA CGG GAC TAA-3' and reverse 5'-CTA TAA AAC CCT TTC CAA TCA TCG TC-3'; with 226bp product.[10] Briefly the PCR protocol includes, initial denaturation at 95°C for 10 min, followed by 45 cycles of 95°C for 15 s, and 60°C for 30 s for combined annealing and extension. Furthermore, transport of strains to reference centers may cause delays in appropriate management and notification to authorities for outbreak investigation. National surveillance is an important step toward understanding the burden of diphtheria in India and only few regional studies have been conducted.[6,10] There have also been reports of penicillin-resistant *C. diphtheriae* which is of

significant concern as laboratory intervention in such cases is imperative.[6] India has a significant task ahead; however, with each case report and policy brief brought to the forefront, it is possible for better control of this deadly vaccine-preventable disease.

Conclusion

Awareness among primary care physicians, widespread universal immunization coverage, availability of modern microbiological support, and rapid early diagnosis are the cardinal steps to the control of diphtheria reemergence.

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Conflicts of interest

There are no conflicts of interest.

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