Adult-onset nasopharyngeal diphtheria: an uncommon but rapidly progressive and potentially fatal infection


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INTRODUCTION

Diphtheria is an ancient disease, with its discovery dating back to the 19th century (Zakikhany & Efstratiou, 2012). It was once a leading cause of death among children worldwide, but its incidence has markedly decreased following the widespread use of diphtheria vaccine and has nearly become a forgotten communicable disease. However, it remains a public health concern in developing countries, including Southeast Asian nations (Jain et al., 2016). In Malaysia, diphtheria vaccination is part of the National Immunisation Schedule for Children and is administered at two, three and five months or age, followed by booster doses at the age of 18 months and at seven years. Despite this, diphtheria appears to be re-emerging not only among children, but also among adults (Isahak, 2000). Due to the highly infectious nature and high fatality rate of diphtheria, even a single reported case constitutes an outbreak (Loganathan & Mohamed, 2018). We report a case of nasopharyngeal diphtheria in a vaccinated young adult which progressed rapidly to multi-organ failure and ultimately death within 48 hours of presentation.

CASE REPORT

A 27-year-old Malay man presented to the emergency department with a four-day history of fever, sore throat, hoarseness of voice, and neck swelling. He claimed to have received all his childhood vaccinations and had no known medical illnesses. During laryngoscopy, a white slough (or membrane) was seen at the base of his tongue. The epiglottis was also bulky and the arytenoids were swollen bilaterally. The membrane was sent to the microbiology laboratory for culture. A diagnosis of nasopharyngeal diphtheria was made clinically and the patient was treated with an anti-toxin together with erythromycin, while awaiting the culture result. Nevertheless, the patient’s condition deteriorated swiftly and although the laboratory eventually confirmed an infection by toxin-producing C. diphtheriae, the patient had already succumbed to the infection.

Keywords: Adult; Corynebacterium diphtheriae; nasopharyngeal; vaccination.
Laboratory investigations demonstrated a high white blood cell count of 15.4 x 10^9/L, with a predominance of neutrophils, and an elevated erythrocyte sedimentation rate of 71 mm/hr. Other serum biochemistry results were normal, except for raised alanine transaminase and aspartate transaminase levels of 104 U/L and 142 U/L, respectively. During laryngoscopy, a white slough membrane was seen at the base of the tongue, the epiglottis was bulky and the arytenoids were swollen bilaterally. The membrane was sent to the microbiology laboratory for culture. Within hours, his symptoms worsened and he became tachypnoeic. His oxygen saturation dropped to 89% despite breathing using a high-flow oxygen mask, necessitating endotracheal intubation. At that moment, the physician made a clinical diagnosis of respiratory diphtheria. He was promptly given 100,000 units of diphtheria anti-toxin (DAT) together with intravenous erythromycin at a dose of 500 mg q6h, and immediately transferred to the isolation ward.

The patient developed multiple hypotensive episodes, acute kidney injury (with a serum urea and creatinine levels of 25.9 mmol/L 458 μmol/L, respectively), metabolic acidosis and worsening of transaminitis. Alas, despite treatment, the patient’s condition deteriorated rapidly. He died of multi-organ failure within 48 hours of admission. The laboratory diagnosis was only obtained from throat swab and pharyngeal membrane cultures following his demise. The initial gram stain from these specimens revealed moderate pus cells, scanty gram positive cocci and moderate gram-positive rods. The gram-positive rods were arranged like “Chinese characters” (Figure 1). The bacteria grew on Hoyle's tellurite medium as black colonies (Figure 2). The catalase-positive bacteria were identified biochemically as *C. diphtheriae* by Vitek ANC (bioMeriux, France) with a %ID of 99% (bionumber: 6323000410405; excellent identification). Diphtheria toxin production was confirmed through an Elek test. The organism was susceptible to erythromycin [minimal inhibitory concentration (MIC): 0.032 μg/mL] but resistant to ceftriaxone (MIC: 4 μg/mL) (CLSI, 2016).

**DISCUSSION**

*C. diphtheriae* is a non-motile gram-positive bacterium with a club-shaped morphology and “Chinese character” arrangement. Humans are the only known reservoirs for *C. diphtheriae*. Infrequently, toxigenic strains of *Corynebacterium ulcerans* and *Corynebacterium pseudotuberculosis* may also cause diphtheria, although these species are of zoonotic origin (Zakikhany & Efstratiou, 2012). Depending on the anatomical site, diphtheria can be categorized as respiratory (when the nasal, pharyngeal and laryngeal cavities are affected), cutaneous or ocular (Sharma et al., 2019). The infection is typically spread through respiratory droplets or close physical contact with cutaneous lesions, although a clear-cut route of transmission was not apparent in our patient. He could have contracted the infection from an asymptomatic carrier. Vaccinated individuals can carry *C. diphtheriae* without symptoms, and in countries with good diphtheria vaccination coverage, they can be potential sources of infection (Jané et al., 2018).

The clinical diagnosis of nasopharyngeal diphtheria can be challenging, particularly if it’s less severe at presentation (Zakikhany & Efstratiou, 2012). It can mimic a host of other infections, namely acute epiglottitis, infectious mononucleosis, oral syphilis, oral candidiasis, and viral as well as bacterial pharyngitis (including streptococcal pharyngitis) (Sharma et al., 2019). The quintessential characteristic of nasopharyngeal diphtheria is a greyish-white pseudo-membrane firmly attached to the pharynx, tonsils or larynx. Fundamentally, this “membrane” is a dense grey debris layer encompassing dead cells, fibrin, erythrocytes, leukocytes and bacteria (Jain et al., 2016). This pseudomembrane played an integral role in the naming of the disease, because “diphtheria” means “a piece of hide leather” in Greek (Zakikhany & Efstratiou, 2012). The typical “bull neck” of nasopharyngeal diphtheria is due to a combination of oedematous mucosa and cervical lymphadenopathy – although observed in only a third of cases, it heralds high mortality (Jain et al., 2016).

If a case cannot be confidently diagnosed on clinical grounds, a laboratory diagnosis should be sought urgently. The usage of a medium containing potassium tellurite (e.g. Hoyle’s tellurite agar) is recommended because it inhibits normal oropharyngeal flora and selects for *C. diphtheriae*, which characteristically produce black colonies.
(Zakikhany & Efstratiou, 2012). However, tellurite agar is costly (compared to the routinely used sheep blood agar) and consequently not well stocked by many diagnostic microbiology laboratories (Loganathan & Mohamed, 2018). While *C. diphtheriae* may also grow on sheep blood agar, this agar is not selective and the growth of normal flora on the agar may hamper the isolation of the pathogen or the culture will simply be reported as “mixed growth” without further testing. Thus, physician-laboratorian communication is vital to increase the likelihood of pathogen isolation; the laboratorian has to be informed by the physician of any suspected diphtheria case during specimen submission.

The major virulence factor of *C. diphtheriae* is a highly potent and lethal exotoxin (DT) which inhibits protein synthesis in human cells (Zakikhany & Efstratiou, 2012). Most diphtheria complications (including death) are attributable to the effects of DT. The tox gene which codes for DT is of bacteriophage origin and highly virulent strains have been found to harbour multiple tox copies in their genomes (Sharma et al., 2019). Such is the prominence of DT in the pathogenesis of diphtheria that its detection ought to be performed whenever *C. diphtheriae* is cultured. For our isolate, this was achieved through the Elek test, which is an agar-based test that works on the principle of antigen-antibody immunoprecipitation. Polymerase chain reaction (PCR) assays which detect tox are also available, but although PCR can potentially shorten the detection time from 24-48 hours to only a few hours, the main drawback is that a positive PCR result does not automatically confirm toxin production. This is because there are non-toxigenic tox-bearing *C. diphtheriae* (NTTB) strains which are genotypically tox-positive, but cannot express DT due to nucleotide mutations or deletions (Sharma et al., 2019). Thus, all tox-positive isolates should still be subjected to the Elek test.

The diphtheria vaccine, along with the pertussis and tetanus vaccines, were the pioneer vaccines used in Malaysia to kick-start the national immunisation programme back in 1960 (Balbir Singh et al., 2019). The diphtheria vaccine coverage in Malaysia is excellent, with a reported coverage of 99% in 2015 (Loganathan & Mohamed, 2018). Thus, we hypothesise that the occurrence of diphtheria in our patient was the result of waned immunity, since booster vaccinations are desirable to facilitate the process. Time is of the essence in managing nasopharyngeal diphtheria, with rapid clinical suspicion, a heads-up by the treating physician is desirable to facilitate the process. Time is of the essence in managing nasopharyngeal diphtheria, with rapid clinical deterioration or even death being genuine concerns. A booster diphtheria vaccination dose every 10 years should also be made a public health policy to lessen the occurrence of adult-onset diphtheria.

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**Conflict of interest**

The authors declare that they have no conflicts of interest.

**REFERENCES**


**CONCLUSION**

Nasopharyngeal diphtheria should neither be forgotten nor neglected, even in regions with good diphtheria vaccine coverage. A high index of suspicion is the cornerstone to its diagnosis: it should be considered when a patient has an adherent greyish-white pseudomembrane in the nasopharynx. When the laboratory is required to confirm a clinical suspicion, a heads-up by the treating physician is desirable to facilitate the process.