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Case Report
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A Case of Acute Diphtheria with Severe Airway Obstruction

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Abstract

Diphtheria infection, once a significant cause of death and morbidity, is now potentially preventable, owing to the diphtheria toxoid vaccine. In developed countries with low disease incidence, a timely diagnosis may be elusive to unsuspecting physicians less familiar with the condition. The authors present the first local case of diphtheria infection in Singapore in 25 years. A 21-year-old Bangladeshi male with no recent travel history was seen with an atypical presentation of infective acute airway obstruction. This case demonstrates the importance for clinicians to remain cognizant of possible causative pathogens in the context of infection, and to maintain an index of suspicion for highly transmissible diseases. In such cases, early and adequate isolation precautions are prudent, with the involvement of multi-disciplinary teams to ensure best supportive care. Prompt notification to the Ministry of Health should also be undertaken.

Keywords: Diphtheria; Bacterial infection; Airway obstruction; Infectious

Introduction

Diphtheria infection, previously a significant cause of death and morbidity, is now potentially preventable, following the advent of diphtheria toxoid vaccine. In countries with low disease incidence, making an accurate and timely diagnosis may prove elusive to the unsuspecting physicians. We present the first local case of diphtheria infection in Singapore in 25 years.

Case Presentation

A 21-year-old Bangladeshi construction worker was brought to the Emergency Department at ten o'clock in the evening, with severe neck and throat pain, and dysphagia. On arrival, he was unable to give a coherent history due to pain. Collateral history from his colleagues revealed no known caustic or foreign body ingestion prior to onset of symptoms. There was no history of trauma or diabetes, and no recent travel history in the preceding three months. He was septic, febrile at 40 degrees Celsius, tachycardia with pulse rate of 140 beats per minute. On pulse oximetry, he was saturating between 90 and 95 percent, on a 10-litre face mask. His blood pressure was 170/80.

The patient appeared exhausted and was unable to speak. His Glasgow Coma Score was 11 (E3 V2 M6). There was generalized swelling and oedema of the entire neck, without discoloration of the overlying skin. Examination of the oral cavity revealed pooling of saliva and oedema over the soft palate, obscuring the tonsils bilaterally.

Flexible nasendoscopy at the resuscitation bay was firstly attempted through the nasal cavity, but quickly abandoned when severe nasal cavity swelling was encountered, rendering it impossible to pass the scope through the anterior nasal space. Strings of pus and slough were seen discharging through both nostrils. Scope through the oral cavity revealed circumferential pharyngeal wall oedema, with large amount of purulent secretions. The supraglottis (epiglottis, aryepiglottic folds) and vocal cords were severely oedematous.

A lateral neck X-ray demonstrated thickening of the prevertebral soft tissue and thumb-printing of the epiglottis. Laboratory tests include total white count of 22.84 × 10^9/L, haemoglobin 15 g/dL. Arterial blood gas performed on 100 percent inspired oxygen showed respiratory acidosis.

Given the clinical impression of an impending airway collapse, the patient was immediately brought into emergency operating theatre, for trial of awake fiber optic intubation, keeping in view tracheostomy. A dose of intravenous co-amoxiclav and dexamethasone was administered.

Intra-operatively, purulent secretions and severe swelling rendered poor visualization of

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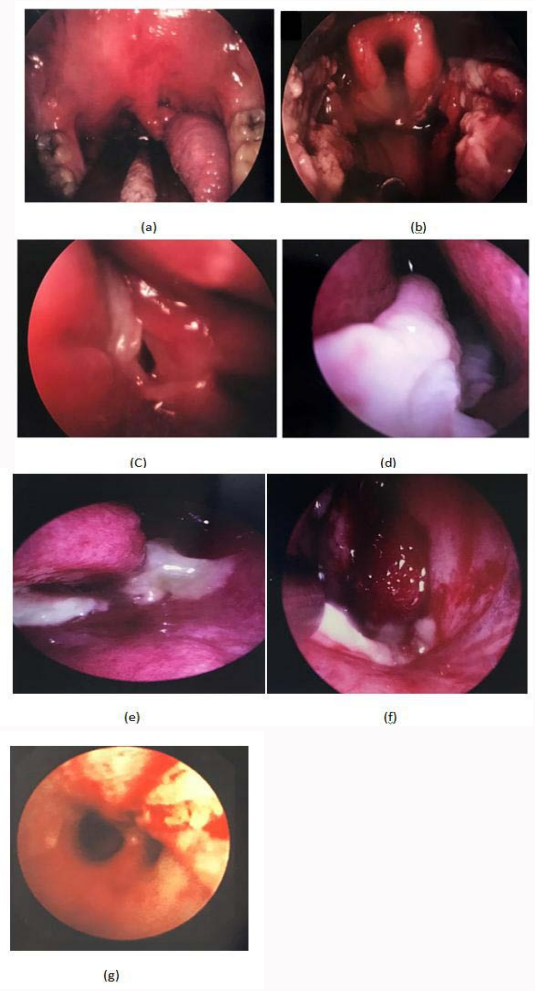

Figure 1: Clinical photos of panendoscopy of the upper aerodigestive tract. (a) Generalized soft tissue oedema of bilateral anterior tonsillar pillars and soft palate. (b) Purulent secretions and pseudomembranous appearance of mucosa over bilateral tonsils, base of tongue and larynx. Tonsils appear necrotic, and the epiglottis oedematous. (c) False and true cords oedema with near-complete airway narrowing. Pseudomembranous deposits were seen within the glottic region. (d,e) Purulent nasal discharge with sloughy pseudomembrane seen in bilateral anterior nasal space. (f) Pseudomembranous deposits extend into the posterior nasal space, with adenoids appearing friable. (g) Flexible bronchoscopy performed through tracheotome down to carina identified similar pseudomembrane along tracheal walls, although less extensive.

the airway. Moreover, the patient's oxygen saturations began to deteriorate. The decision was made to convert to tracheostomy. The trachea was central, with overlying soft tissue oedema. Fibrinous material was encountered during dissection down to the trachea.

Following the securing of airway, a panendoscopy was performed, given the unusual clinical picture of fibrinous deposits (Figure 1). Purulent secretions with a pseudomembranous appearance of the mucosa were seen over bilateral tonsils, which appeared necrotic. There was oedema around the uvula, extending to the anterior tonsillar pillars bilaterally and to the soft palate. The base of tongue, epiglottis, pyriform fossae, aryepiglottic folds and vocal cords were also involved, with similar pseudomembranous debris found at the level of glottis and subglottis. In the anterior nasal space, purulent discharge with sloughy pseudomembranous material was seen extending into the post-nasal space. Mucosa over the adenoids was friable and necrotic. Samples were obtained for histology, aerobic, anaerobic, fungal culture and sensitivities, as well as acid-fast bacilli smear and culture. Flexible bronchoscopy through the tracheostomy was performed down to carina-similar pseudomembranous deposits were identified along the tracheal walls, albeit less extensive. Beyond the cricopharyngeus, there was no clinical evidence of disease. Rigid oesophagoscopy down to 25 cm of the cervical oesophagus was notably unaffected by the pseudomembranous deposits as compared to the extensive involvement of the airway.

The intra-operative findings prompted the suspicion of diphtheria infection. Following tracheostomy and panendoscopy, the patient was escorted to the radiology department; airborne precaution was undertaken in view of the suspicion of a transmissable infectious disease. Computed Tomography (CT) of the neck revealed diffuse inflammatory soft tissue thickening involving the upper aerodigestive tract, with near-complete airway narrowing. There was no loculated rim-enhancing collection. Tracheostomy tube was in-situ (Figure 2).

The patient was then escorted to the surgical intensive care unit, where he received ionotropic and ventilator support overnight. He received medical and nursing care all while being placed on airborne precaution. He remained drowsy the following morning-12 h following admission. An urgent consult with the Infectious Disease team validated the clinical suspicion of diphtheria. Recommendations included diphtheria anti-toxin and intravenous erythromycin. The Ministry of Health was notified with regards to a suspected case of diphtheria infection. Electrocardiogram showed tall T waves across the anterior chest leads; cardiac enzymes were unremarkable.

Within 36 h following his admission, the patient's oxygen requirement escalated to require maximal ventilatory support. Interval chest X-ray revealed bilateral pulmonary infiltrates (Figure 3). A bedside echocardiogram revealed normal ventricular functions, with no demonstrable regional wall abnormality.

The patient developed acute respiratory distress syndrome. He was put on prone ventilation, with antibiotics escalated to intravenous piperacillin/tazobactam. The patient was deemed unstable for transfer to another unit that could provide extracorporeal membrane oxygenation. Intra-operative tissue cultures confirmed *Corynebacterium diphtheriae*; the Ministry of Health was again notified, and contact tracing was initiated.

On the fourth night-within 75 h of hospital admission, the patient collapsed with only transient response to cardiopulmonary resuscitation. There was no detectable oxygen saturation on pulse oximetry, despite nearly two hours of resuscitation. Shortly after, the patient passed away (Figure 4).

Clinical Presentation

There are two forms of diphtheria infection - respiratory and cutaneous [5]. They are mostly caused by toxigenic strains of *C. diphtheriae*. The incubation period of the disease ranges between one and 10 days. In early stages, patients develop a sore throat and fever, which may progress to either or both types of diphtheria infection. Patients previously vaccinated against the infection may experience milder infections, resembling a strep throat infection, while carriers being completely asymptomatic [3].

In respiratory diphtheria, mucopurulent nasal discharge, sore nostril with crusting may be evident [3]. There may pharyngitis, cervical lymphadenitis with associated soft tissue swelling, resembling a 'bull neck' appearance. Paralysis of palatal muscles, resulting in

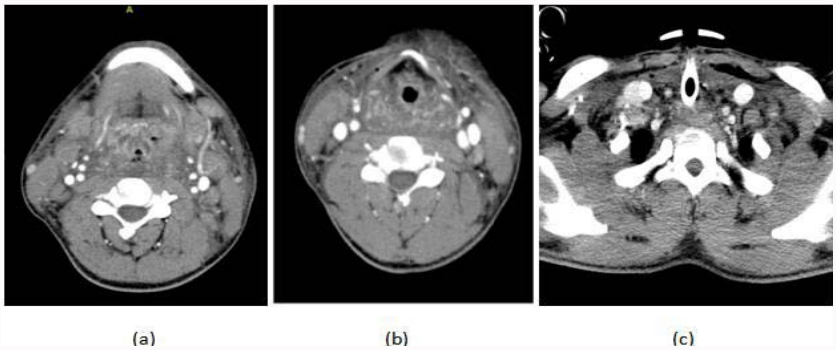

Figure 2: Contrasted axial Computed Tomography of neck. (a) Inflammatory soft tissue thickening and oedema involving oropharynx, pharyngeal mucosal space, retropharyngeal region, and severe narrowing of the supraglottic laryngeal airway. (b) Diffuse hypodensity in the retropharyngeal and pharyngeal mucosal space suggestive of generalized oedema, with subcutaneous fat stranding. No rim-enhancing collection visible. (c) Tracheostomy tube *in-situ*.

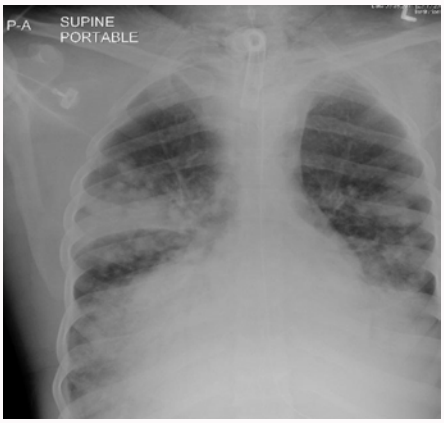

Figure 3: Chest radiograph demonstrating bilateral patchy pulmonary infiltrates.

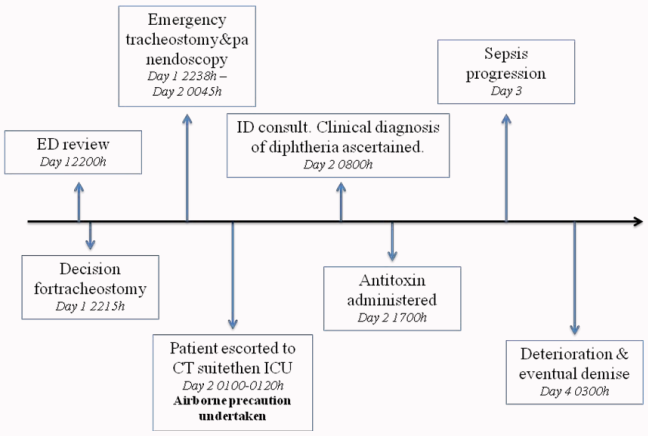

Figure 4: Timeline demonstrating the patient's rapid clinical deterioration with progression of sepsis.

dysphagia, as well as acute airway compromise may also be seen [3].

The second form of diphtheria infection–the cutaneous type–is actually the predominant clinical manifestation [5]. Cutaneous diphtheria follows a mild–but chronic–course. Skin vesicles and pustules form, typically on the extremities, and quickly rupture before forming a 'punched-out' ulcer. These lesions can be tender for weeks, coated with pseudomembrane, which then breaks apart to reveal an exudative base. Cutaneous diphtheria usually heals over two to three months, leaving a hollow scar [5].

Management of diphtheria infection

The diagnosis of diphtheria infection is largely driven by clinical suspicion. While waiting for definitive culture and sensitivities, antibiotics and anti-toxin should be administered, to reduce morbidity and mortality associated with the disease. Macrolides such as erythromycin and azithromycin, as well as penicillin's are antibiotics of choice against the infection [3]. A dose of diphtheria anti-toxin should also be administered at the earliest possible time [3]. Patients should be isolated, and droplet precautions taken. It is accepted that the disease is no longer contagious 48 h following initiation of treatment. Elimination of the pathogen should be proven with two consecutive negative cultures following antibiotics completion [3]. In the convalescent stage, patients should receive a booster, as it is thought that clinical infection may not always induce adequate levels of anti-toxins.

Notification and contact tracing are also paramount in the management of diphtheria infection. As with any notifiable disease, the Ministry of Health should be notified with any suspicion of the disease, while waiting for definitive cultures. Contacts of diphtheria are given a course of antibiotics prophylaxis, with aims to eradicate incubating illness, as well as to prevent carriage to others. For close contacts-namely household contacts-a diphtheria toxoid booster should be administered [3].

Complications

As demonstrated in our case, airway obstruction secondary to pseudomembranous deposits and extensive parapharyngeal oedema may pose an immediate threat to patients with severe disease. Severe sepsis secondary to overwhelming infection also has its own sequelae; we witnessed the unfortunate case of respiratory failure and eventual demise in our reported case. Survivors of the acute-phase infection may be affected by neuritis-this occurs in up to 10% to 20% of patients within the first 10 days. Interference of nervous supply to the soft palate muscles results in dysphagia, nasal speech and regurgitation. Involvement of the diaphragm may take up to two months to manifest; respiratory failure ensues. Ocular and peripheral nervous involvement may take up to months to declare itself.

Myocarditis usually presents within the first two weeks of illness. During which, the pharyngeal symptoms would have improved, if not fully resolved. Tachycardia disproportionate to fever, heart blocks and congestive heart failure are common presentations. Of note, myocardial involvement is associated with a high mortality rate,

accounting for half of all deaths of diphtheria infection [3].

Without treatment, death rates from the illness were high at 50% [3]. With the advent of antibiotics, case-fatality rates are now at 5% to 10% [3]. For those who survive through the course of the illness, they tend to have a complete recovery from the neurological insults and cardiac complications.

Challenges faced at present day

Despite high childhood immunization rates in developed countries, circulation of the disease persists. An asymptomatic carrier state exists even among immunized individuals, hence posing a challenge in eliminating disease carriage within the community [3]. Immunity against diphtheria infection wanes over time; adults lose protection from childhood vaccines unless they receive boosters [3]. It is recommended that individuals at high risk of exposure (i.e. travelers to endemic areas, laboratory and healthcare workers) should receive a booster every 10 years [3]. This renders a significant proportion of older adults potentially susceptible to the illness, in both developed and developing countries.

In developed countries where there is low disease incidence, the diagnosis may not be considered by the unsuspecting clinicians. Furthermore, the use of prior antibiotics before obtaining samples for cultures can preclude recovery of the organism [3]. Despite diphtheria being a 'centuries-old' illness, it appears that there may be still limited epidemiological, clinical and laboratory expertise in the condition. This case demonstrates that with an unusual clinical presentation in the context of infection, clinicians should maintain an index of suspicion for highly transmissible diseases, which may be caused by less commonly encountered pathogens. Early and adequate isolation precautions should be undertaken, together with prompt notification to the Ministry. Finally, the involvement of multi-disciplinary teams is prudent to optimize patient care.

Discussion

The impact of diphtheria infection

The Hippocrates first described Diphtheria in the 4th century B.C., with major epidemics having swept across Europe in the 17th century. It was known as 'the strangling angel of children'. It comes from the Greek word 'Diphtheria', meaning leather, used in describing the grayish pseudomembrane the bacteria deposits on mucous membranes. The causative organism is *Corynebacterium diphtheriae*, a gram-positive, aerobic, non-motile rod, which is only pathogenic in humans [1].

Diphtheria was a leading cause of childhood death in the pre-vaccine era [2]. Following the invention of the diphtheria toxoid vaccine in 1923, and its large-scale use in industrialized countries in the 1940s to 1950s, there was a continuous decline in incidence [2]. According to the Centers for Disease Control and Prevention (CDC), 206,000 cases of diphtheria were reported in 1921, with 15,520 resultant deaths [3]. Before treatment for diphtheria was made available, mortality was high at up to 50% [3]. These numbers contrast starkly to the post-vaccine era; in the last 10 years, less than five cases of diphtheria infection in the United States were reported to the CDC [3]. Nonetheless, the disease remains a global burden. In 2014, over 7,000 cases were reported to the World Health Organization (WHO), with estimations that many more went unreported [3].

Diphtheria mostly prevails in epidemics [2]. The last disease outbreak was in Afghanistan, with 50 reported cases, and three deaths [2]. India, Indonesia and Nepal were countries with the highest case counts for the preceding 15 years [2]. It is believed that poor surveillance and under-reporting in certain countries, such as Nigeria, means that there is an underestimation of the true disease incidence [2]. Madagascar and Papua New Guinea were among the other countries that experienced large outbreaks over the last decade [2].

The diphtheria vaccine

The WHO recommends a first three primary series; after which, immunization schedules for vaccinating against diphtheria infection are dependent on the country context. Vaccination schedules vary widely across the globe, pertaining to both the number of booster doses, and the ages at which these boosters are given [2]. From currently available literature, 25% of the world administers only the first three primary series, with another 25% recommending three booster doses following the initial three series [2].

In Singapore, the last local case of diphtheria infection was reported in 1992, with an imported case last seen in 1996 [4]. Since 1962, diphtheria and measles immunization were made compulsory by law, as part of the National Childhood Immunisation Programme [4]. Three primary series are administered at three, four and five months of age. Three further boosters are administered at 18 months, 6 to 7 and 11 to 12 years of age [4]. The estimated coverage for 2-year-olds is at 96 to 98 percent at present [2].

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