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Case Report

Nasal diphtheria (chronic carriage) caused by nontoxigenic *Corynebacterium diphtheriae*

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ABSTRACT

Toxigenic strains of *Corynebacterium diphtheriae* cause the majority of respiratory diphtheria cases. However, nontoxigenic strains of *C. diphtheriae* can also cause diseases, and have become increasingly common. Infection that is limited to the anterior nares (nasal diphtheria) is a well-described but rare condition, even for toxigenic *C. diphtheriae*. We report a case involving chronic carriage of nasal diphtheria caused by nontoxigenic *C. diphtheriae*, as well as a review of other reported nontoxigenic *C. diphtheriae* cases in Japan. Mild or asymptomatic nasal diphtheria involving nontoxigenic strains, which can be the source of transmission, may be underrecognized. Our case highlights the importance of awareness regarding nontoxigenic diphtheria among clinicians, especially in the era of improved diphtheria vaccination coverage.

1. Introduction

Diphtheria is an infection caused by *Corynebacterium diphtheriae*, which is a nonsporulating, uncapsulated, nonmotile, Gram-positive bacillus. It typically affects the respiratory tract (respiratory diphtheria), and can involve asymptomatic carriage, but can also cause cutaneous and invasive diseases. During the pre-immunization era, diphtheria was a common infection among children and was associated with a high mortality rate. However, it has become relatively rare in developed countries that have introduced toxoid immunization, although diphtheria remains endemic in south and southeast Asian developing countries [1]. Classically toxigenic strains of *C. diphtheriae* are the causative agent in most cases, although nontoxigenic strains of *C. diphtheriae* and toxin-producing strains of *Corynebacterium ulcerans* can also cause diseases. We report a case involving chronic carriage of nasal diphtheria caused by nontoxigenic *C. diphtheriae* in a patient from an endemic area (Nepal).

2. Case report

A 24-year-old Nepalese man with no medical history presented with a 3-day history of fever, headache, productive cough, and hemoptysis. He denied experiencing nasal discharge, pain, congestion, or epistaxis. He had moved from Nepal to Tokyo (Japan) 2 years before the presentation and had never returned to Nepal. He was not receiving any medication, had received all recommended vaccinations (including the diphtheria vaccine during childhood), and his family history was unremarkable. A physical exam only revealed fine crackles and wheezes in the right lower lung field, and no abnormal skin lesions were observed. Chest radiography and computed tomography revealed patchy nodular consolidation in the right upper and middle lobes. Empiric treatment using oral cefcapene pivoxil was started, and we observed improvement of his fever and productive cough during the following days. Follow-up chest radiography also revealed

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improvement of the consolidation. The initial sputum sample was cultured using sheep blood agar (Nissui Pharmaceutical, Japan), chocolate II agar (Becton, Dickinson and Company, US), and modified DRIGALSKI agar (Nissui Pharmaceutical, Japan), which revealed pleomorphic Gram-positive bacilli (Fig. 1A), as well as white blood cells, Gram-positive cocci, Gram-negative cocci, and Gram-negative bacilli. After 18 h of incubation at 35 °C, growth of small light gray colonies was observed. Neisser staining of the isolate revealed metachromatic granules (polar bodies, Fig. 1B). The isolate was identified as *C. diphtheriae mitis*/*belfanti* using the API Coryne identification system (bioMérieux, France). Further molecular analyses using sequencing of the 16S rRNA and *rpoB* genes confirmed the isolate's identification, with approximately 820 base pairs and 430 base pairs sequenced for the 16S rRNA and *rpoB* genes, respectively, and analyzed using the GenBank and DNA Data Bank Japan databases. The primer sequences have been previously reported [2,3]. The top 20 matched species were all *C. diphtheriae* with a more than 98% homology. In addition, we detected the *DtxR* gene, which is specific for *C. diphtheriae* [4], although the specific biotype could not be determined (*C. diphtheriae mitis* or *belfanti*). Furthermore, the identification was confirmed with matrix-assisted laser desorption/ionization-time of flight mass spectrometry (Bruker, Germany). Antimicrobial susceptibility testing was performed using a broth microdilution method, which revealed that the isolate was susceptible to penicillin, cefotaxime, meropenem, clindamycin, erythromycin, minocycline, levofloxacin, and vancomycin according to Clinical and Laboratory Standard Institute breakpoints [5]. Furthermore, the isolate was found to be a nontoxigenic strain based on testing using polymerase chain reaction for the diphtheria toxin gene (*tox*) and the Elek test for toxin production [6,7]. In addition to *C. diphtheriae*, we identified *Klebsiella oxytoca* and *Klebsiella pneumoniae* subsp. *ozanae* in the initial sputum culture.

As *C. diphtheriae* rarely causes pneumonia, we investigated other possible sources of the *C. diphtheriae* infection. Magnetic resonance imaging of the head revealed findings suggestive of sinusitis in the right maxillary, ethmoid, and sphenoid sinuses. A subsequent fiberscopic examination revealed nonspecific encrusted lesions in the right nasal middle turbinate, middle meatus, and septum, which were located close to the maxillary sinus ostium (Fig. 2). No pathological changes were observed in the pharynx and larynx. Multiple samples of the nasal lesion were cultured, and growth of *C. diphtheriae* was observed, although no growth was observed in the throat sample culture. Therefore, nasal diphtheria was suspected.

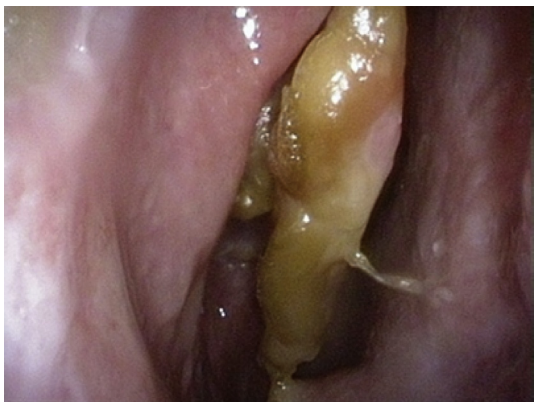

Fig. 2. A fiberscopic examination revealed nonspecific encrusted lesions in the right nasal turbinates.

The patient also experienced concomitant chronic sinusitis, which might have been caused by blockage of the maxillary sinus ostium. The patient's acute bacterial pneumonia was thought to be caused by non-*C. diphtheriae* organisms for several reasons. First, the sputum sample appeared to be contaminated with oral and nasal secretions. Second, there was polymicrobial growth in the culture. Third, nontoxigenic *C. diphtheriae* has rarely been reported to cause pneumonia. Thus, we began treating the patient using oral amoxicillin and azithromycin. Repeated fiberscopic examination at 1.5 months after treatment revealed persistent encrusted lesions in the right turbinates, although the samples from the right naris did not grow *C. diphtheriae*. The patient was subsequently lost to follow-up.

3. Discussion

Although carditis and motor neuropathy are notoriously associated with circulating diphtheria toxins, the respiratory tract is the most commonly affected system in diphtheria cases, with the posterior mouth and proximal pharynx being the most common infection sites. The classic “pseudomembrane” is often observed as a result of toxin production, and infection limited to the anterior nares (nasal diphtheria) is a well-described but rare condition [8–10]. Anterior nasal infection typically presents with mild symptoms, such as serosanguinous or seropurulent nasal discharge, which are often associated with subtle whitish patches on the mucosal membrane of the septum [11]. However, according to the

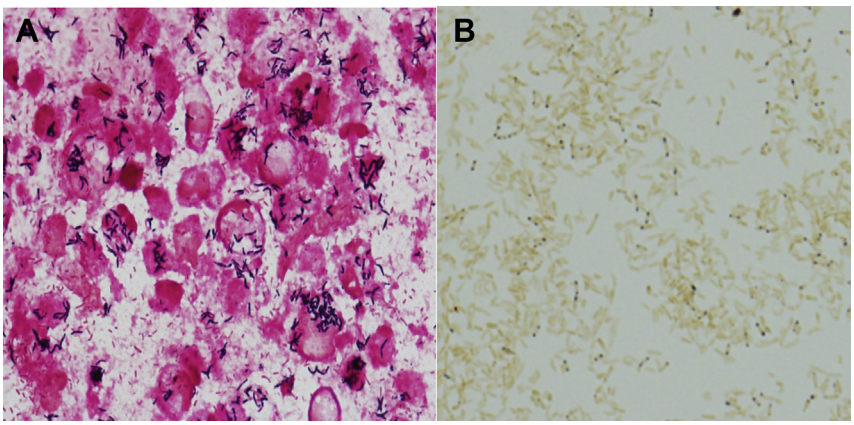

Fig. 1. (A) Gram staining of the initial sputum sample revealed pleomorphic Gram-positive bacilli. (B) Neisser staining of the isolate revealed metachromatic granules (polar bodies).

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