A Case of Necrotizing Epiglottitis Due to Nontoxigenic *Corynebacterium diphtheriae*

Jessica A. Lake, MD, MPH[a], Matthew J. Ehrhardt, MD, MS[b], Mariko Suchi, MD, PhD[c], Robert H. Chun, MD[d], Rodney E. Willoughby, MD[e]

abstract

Diphtheria is a rare cause of infection in highly vaccinated populations and may not be recognized by modern clinicians. Infections by nontoxigenic *Corynebacterium diphtheriae* are emerging. We report the first case of necrotizing epiglottitis secondary to nontoxigenic *C diphtheriae.* A fully vaccinated child developed fever, poor oral intake, and sore throat and was found to have necrotizing epiglottitis. Necrotizing epiglottitis predominantly occurs in the immunocompromised host. Laboratory evaluation revealed pancytopenia, and bone marrow biopsy was diagnostic for acute lymphoblastic leukemia. Clinicians should be aware of aggressive infections that identify immunocompromised patients. This case highlights the features of a reemerging pathogen, *C diphtheriae*.

Departments of [a]Pediatrics, [c]Pathology, [d]Otolaryngology, and [e]Infectious Disease, Medical College of Wisconsin, Milwaukee, Wisconsin; and [b]Department of Oncology, St Jude Children's Research Hospital, Memphis, Tennessee

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Address correspondence to Jessica Lake, MD, MPH, Department of Pediatrics, 8701 W Watertown Plank Road, Milwaukee, WI 53226. E-mail: jelake@mcw.edu

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Diphtheria was once a major cause of death and disability in children. In the 1920s, the United States saw up to 200 000 cases and nearly 15 000 deaths per year due to diphtheria.[1] After the development and routine use of diphtheria toxoid in vaccines in the 1940s, toxigenic diphtheria became a rare infection in the United States, with only 5 cases reported between 2000 and 2012.[1] Worldwide, toxigenic diphtheria remains endemic in countries with low vaccination coverage, including 7088 cases reported in 2008.[1,2] In the early 1990s, 157 000 cases and >5000 reported deaths occurred in the Soviet Union.[1,2] As recent as 2013, an outbreak occurred in a resettlement camp in Kandahar, Afghanistan, resulting in 50 cases and 3 deaths[1–3] Seventy-four percent of the cases in Afghanistan were in children ages 5 to 14.[3] Severe disease is most often seen with toxigenic diphtheria but can be seen with the non–toxin-producing form, especially in immunocompromised patients or those with predisposing conditions, such as intravenous drug users and homeless people.

Ten cases of necrotizing epiglottitis have been reported in the literature, 3 of them occurring in children.[4–13] We describe the first reported case of necrotizing epiglottitis in a child infected by nontoxigenic *Corynebacterium diphtheriae*.

CLINICAL RECORD

A 3-year-old, previously healthy girl presented with fever, poor oral intake, fatigue, and sore throat. Examination was notable for cervical adenopathy. Streptococcal antigen and Monospot tested negative. The next day the child developed tender submandibular swelling, drooling, halitosis, and a high-pitched voice. Laboratory evaluation revealed a white blood cell count of 300 cells/μL (reference range 4000–12 000 cells/μL), absolute neutrophil count of 0 (reference range 3000–8000 cells/μL), hemoglobin 8.0 g/dL (reference range 11.5–14.5 g/dL), and platelets 125 000 cells/μL

(reference range 150 000–450 000 cells/μL). Cervical radiographs identified prevertebral soft tissue prominence. The patient was transferred to our pediatric center for additional evaluation and management.

Growth parameters were appropriate for age. Her vaccinations were current with the recommended guidelines, including diphtheria, tetanus, and acellular pertussis vaccinations at 2, 4, 6, and 18 months.[14] Vital signs revealed tachycardia and tachypnea. Examination was significant for an afebrile, ill-appearing child with prominent neck swelling and left neck redness. She had conjunctival erythema, cracked, red lips, and bilateral tonsillar exudates. Cervical nodes were tender and not fluctuant. Plantar desquamation was present. She did not have stridor, respiratory distress, cardiac murmur, or organomegaly. The remainder of the examination was normal. Additional laboratory evaluation revealed fibrinogen of 1116 mg/dL (reference range 200–400 mg/dL) and ferritin of 223 ng/mL (reference range 10–60 ng/mL) with normal lactate dehydrogenase, uric acid, and triglycerides. She was empirically started on vancomycin and cefotaxime. Computed tomography (CT) scans of the neck demonstrated a retropharyngeal collection measuring 7.8 mm in thickness extending down behind the larynx, with prominent bilateral posterior triangle lymphadenopathy indicating retropharyngeal abscess (Fig 1).

On hospital day 2, the patient developed progressive hypoxemia, drooling, and stertor. She was electively intubated in the operating room. White membranes on the laryngeal surface of the epiglottis and left tonsil, compatible with necrosis, were debrided (Fig 2). Pathology of the left tonsil revealed extensive coagulative necrosis and invading cocci and filamentous bacteria without evidence of a pseudomembrane. Culture of the excised left tonsil grew *Prevotella bivia* and few *Haemophilus influenzae*. A bone marrow biopsy revealed atypical lymphoid aggregates consistent with B-cell lymphoblastic leukemia (B-ALL). The patient began induction chemotherapy with dexamethasone, PEG-asparaginase, and vincristine for National Cancer Institute standard risk B-ALL.[15] *C diphtheriae* was identified via phenotypic testing in combination with 16s ribosomal DNA sequencing from a nasopharyngeal culture. She needed persistent cardiopulmonary support, and an echocardiogram was performed, demonstrating reduced cardiac function. She was treated with penicillin and diphtheria antitoxin. Before treatment, titers for diphtheria and tetanus were measured and within the established protective levels after vaccination. Polymerase chain reaction analysis of the isolate and an Elek test, an in vitro assay for toxigenicity, were performed at the Centers for Disease Control and Prevention and confirmed nontoxigenic *C diphtheriae,* biotype *belfanti*. The patient was extubated after 2 weeks and discharged from the hospital after a 1-month hospitalization.

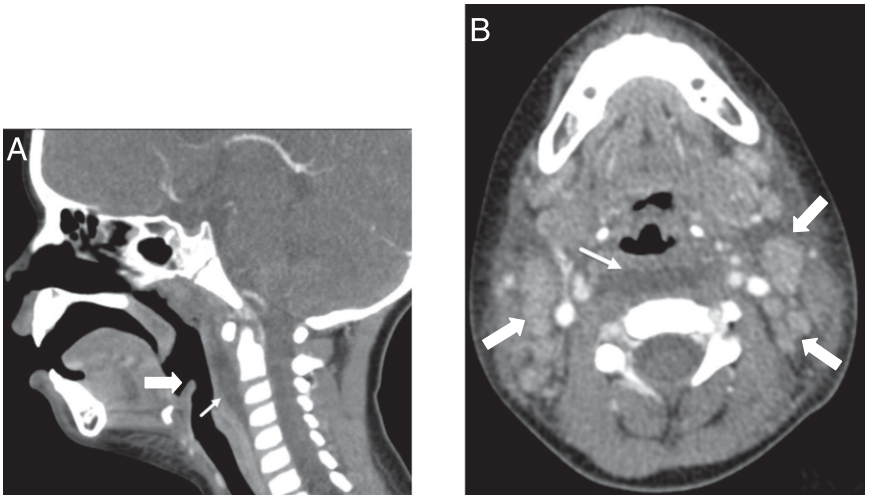

FIGURE 1
A, Postcontrast sagittal CT scan of the neck revealing retropharyngeal edema (thin arrow) and a normal-appearing epiglottis (thick arrow). B, Postcontrast axial CT scan of the neck with retropharyngeal edema (thin arrow) and enlarged bilateral lymph nodes (thick arrows).

DISCUSSION

Case series from Russia and the United Kingdom document outbreaks of severe disease and deaths associated with nontoxigenic *C diphtheriae*, suggesting that this is an emerging disease.[2,16,17] Although our case involved infection of the respiratory tract, severe respiratory

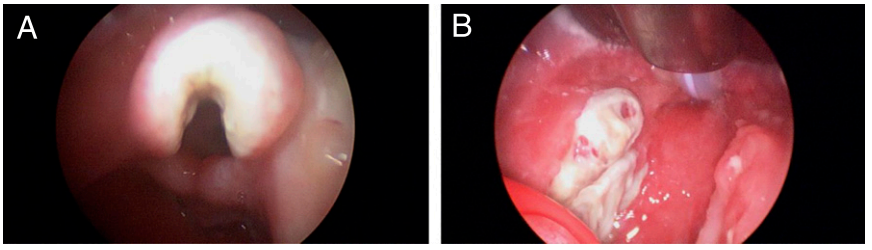

FIGURE 2
A, White membranes on laryngeal surface of the epiglottis. B, White membranes on the left tonsil.

infections due to nontoxigenic *C diphtheriae* are rare. A case of afebrile pneumonia was described in Japan in 2009 in a 60-year-old, ventilator-dependent woman with amyotrophic lateral sclerosis.[18] Additional, severe clinical manifestations, such as endocarditis and arthritis, have been reported. In the 1990s, Western Europe saw multiple cases of endocarditis, arthritis, and osteomyelitis from nontoxigenic *C diphtheriae,* mostly in injection drug users and homeless people.[19]

C diphtheriae is an aerobic gram-positive bacillus that becomes toxigenic when the bacillus is lysogenized by a bacteriophage virus containing the *tox* gene.[1] There are 4 biotypes of *C diphtheriae: gravis, intermedius, mitis,* and a more recently discovered *belfanti*.[1,20] Three biotypes have toxin-forming potential, but only nontoxigenic isolates of *belfanti* have been described.[21] Commonly reported subtypes of nontoxigenic disease include *gravis* and *belfanti,* the latter of which may have a selective advantage by tropism for the respiratory tract and the subtype seen in our patient.[2,20] The reported cases from Western Europe and Japan all isolated biotype *mitis*.[18,19]

There have been no reports of *C diphtheriae* causing necrotizing epiglottitis, a syndrome that clinically overlaps with diphtheria. Necrotizing epiglottitis is exceptionally rare, with only 10 reported cases.[4–13] All but 1 of these cases occurred in an immunocompromised patient.[7] Three cases of necrotizing epiglottitis have been reported in children, all immunocompromised, including a 17-year-old pregnant girl with infectious mononucleosis, a 5-year-old boy with hemophagocytic lymphohistiocytosis, and an infant infected with cytomegalovirus and HIV.[4–6] Surgical management includes airway protection, debridement of necrotic tissue, and cultures of tissue with pathology. Although debridement of the epiglottis may lead to postoperative dysphagia, the goals of surgery are eradication and diagnosis of disease. All 3 children survived their infections, although the first case resulted in a spontaneous abortion and loss of the epiglottis. In our case and the 5-year-old reported in the literature, both children postoperatively had no aspiration and had mild dysphagia that improved in both cases. Our patient had occult B-ALL with absolute neutropenia and therefore was also immunocompromised. She was fully immunized. Diphtheria vaccines protect against the toxin responsible for pseudomembranes, myocardiopathy, and peripheral neuropathy and are 97% efficacious.[1,16] Vaccines do not protect against colonization by nontoxigenic *C diphtheriae*.[22]

Although the toxin is the main virulence factor, the increase in invasive infections due to nontoxigenic *C diphtheriae* suggests that other factors, such as those involved in bacterial adhesion, colonization, or the evasion of host defenses, also contribute to virulence.[16,23] Nontoxigenic *C diphtheriae* are present in asymptomatic carriers and can convert to the toxigenic form if lysogenized by a bacteriophage with the *tox* gene.[16,20] Although this conversion is possible, the increase in severe infections due to nontoxigenic diphtheria over the last 25 to 30 years has not been accompanied by a rise in the toxigenic form.

CONCLUSIONS

Nontoxigenic *C diphtheriae* is an emerging pathogen in some countries, independent of regional vaccination coverage. The vaccine does not protect against nontoxigenic diphtheria. The current case highlights the occurrence of necrotizing epiglottitis suggesting an underlying immunodeficiency, ultimately resulting in the diagnosis of leukemia. It also underscores *C diphtheriae* as a potential cause of life-threatening infection in an immunocompromised patient. Prompt recognition of impaired immunity in the presence of an aggressive infection and tissue culture and diagnosis are critical to good outcomes, as exemplified by this report.

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ABBREVIATIONS

B-ALL: B-cell lymphoblastic leukemia
CT: computed tomography

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