□ CASE REPORT □

Exacerbation of Tracheobronchitis due to Nontoxigenic *Corynebacterium Diphtheriae*

Shunji SHINAGAWA, Masaki FUJIMURA*, Keiichi MIZUHASHI, Shigeo TAKAHASHI, Yatsugi NODA, Takae HIRONE and Tamotsu MATSUDA*

This is the first case report of exacerbation of tracheobronchitis due to nontoxigenic corynebacterium diphtheriae in which tracheal pseudomembrane was identified and oral erythromycine therapy was very successful.
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Key words: sinobronchial syndrome (SBS), mucociliary transport, pseudomembrane, erythromycin (EM), and low dose and long term EM therapy

Case Report

A 54-year-old woman was admitted to our hospital on February 7, 1994, with persistent productive cough, sore throat, and bloody sputum. She had realized an exacerbation of cough and mucopurulent sputum about 2 months prior to admission and had had bloody sputum on January 31. The patient had been in her usual state of health, with productive cough and postnasal drip for a few years; she had thought her symptoms were typical usual and thus she never visited a doctor. The physical examination on admission revealed her to be almost normal. Posterior rhinoscopy revealed mucopurulent postnasal drip and nasal polyps. The laboratory data on admission were as follows. White blood cell count was 3,200/μl; erythrocyte sedimentation rate, 28 mm/hr; CRP 0.2 mg/dl. Serum IgG 2433 mg/dl, IgA 735 mg/dl, IgM 195 mg/dl, IgE 197 mg/dl, and cold hemagglutination ×128 were determined. The CPK level was 37 IU/*l* and the electrocardiogram was normal. Chest X-ray revealed no significant findings. Bronchoscopy on admission revealed diffuse tracheobronchitis and grayish fibrinous exudate over the tracheal mucosa from just below the vocal cord to the first carina (Fig. 1). It was very thick and blocked the lumen of the airway. It was difficult to remove by suction and the biopsy specimens revealed no bronchial neoplasm. Based on these findings we tentatively diagnosed this case as tracheal tuberculosis (1) complicated with chronic sinobronchitis, which we call sinobronchial syndrome (SBS) (2) in Japan. The patient began taking oral erythromycin (EM) 600 mg a day (low dose, long-term erythromycin therapy) (3, 4) for SBS and 1g cephazolin sodium (CEZ) intravenously every 12 hours only for 2 days for prophylaxis of iatrogenic infection following bronchoscopy. From the smear of sputum and bronchial lavage fluid we detected gram-positive rods and *Klebsiella ozaenae* but did not detect *Mycobacterial* species. After 3 days of oral erythromycin therapy, she recovered from severe illness and on day 5 of hospitalization her complaints were almost completely relieved. On day 7 follow-up bronchoscopy revealed only mild tracheobronchitis, no grayish exudate, and no stenotic lesions. On the same day, the gram-positive rods cultured from bronchial lavage fluid obtained on admission were proven to be *Corynebacterium diphtheriae (mitis)*.

Biological characteristics of the bacteria were as follows: glucose (+), maltose (+), sucrose weakly (+), lactose (–), mannitol (–), xylose (–), urease (–), nitrate reduction (–), esculin (+), catalase (+), motility (–), betahemolysis weakly (+), and metachromatic granules (+) were determined. The minimum inhibitory concentrations (MIC) of EM and CEZ against the isolated organism were 0.05 and 0.39 μg/ml respectively. The MIC of CEZ against *Klebsiella ozaenae* were previously reported as 6.25 μg/ml (5). EM was not sensitive against *Klebsiella ozaenae*.

Thereafter she denied systemic complications associated with exotoxin of *C. diphtheriae*. On day 14 of hospitalization the bacteria was definitely identified as nontoxigenic *C. diphtheriae (mitis)* by Elek's test and Microcell culture method at Toyama Hygienic Research Institute. Further, as we could not detect the bacteria from frequent surveillance culture, she was discharged on day 19 of hospitalization and has done well

From the Department of Internal Medicine, Toyama Rosai Hospital, Uozu and *the Third Department of Internal Medicine, Kanazawa University School of Medicine, Kanazawa

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Reprint requests should be addressed to Dr. Shunji Shinagawa, the Third Department of Internal Medicine, Kanazawa University School of Medicine, 13-1 Takara-machi, Kanazawa 920

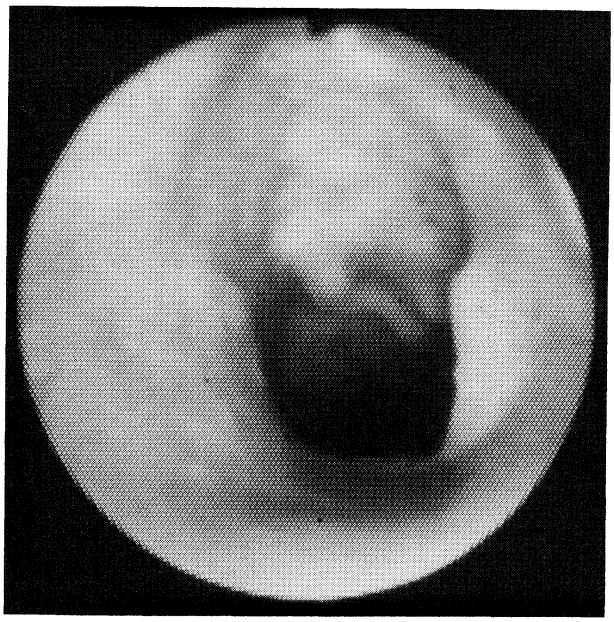

Figure 1. Grayish pseudomembrane covering tracheal mucosa, documented by bronchoscopy on admission.

at the outpatient clinic.

Discussion

Diphtheria is an acute, contagious, febrile illness caused by *C. diphtheriae* (6). The disease is characterized by a combination of local inflammation with pseudomembrane formation of the oropharynx and damage to the heart and peripheral nerves caused by action of its potent exotoxin. An association between complete immunization of the population and a decrease in the incidence of diphtheria has been noted in developed countries (7). Nontoxigenic strains of *C. diphtheriae* are commonly isolated from carriers, particularly during a diphtheria outbreak. Such strains may cause pharyngitis but do not produce the systemic manifestation of diphtheria.

The term of sinobronchial syndrome (SBS) (2) is commonly used by Japanese thoracic physicians, is defined as a coexisting pathology of chronic sinusitis and nonspecific inflammatory lesion of the lower airway (e.g. chronic bronchitis, diffuse bronchiectasis, diffuse panbronchiolitis). Nondiphtherial corynebacteria have been reported rather than *C. diphtheriae* because they are causative organisms of severe infection in both the immunocompromised and immunocomponent hosts (8–11).

The present case is the first report of exacerbation f tracheobronchitis due to nontoxigenic *C. diphtheriae* in a healthy woman. It was diagnosed by bronchoscopy and bacteriological examination of bronchial lavage fluid. Dobie et al (12) reported clinical features of 44 culture-confirmed cases of diphtheria involving the respiratory tract. Sore throat was present in almost all patients and it was the chief complaint in 71% of the cases. Less frequently encountered symptoms were dyspnea, nasal obstruction, and hemoptysis. Twenty-three (54.8%) of 42 patients had a diphtheric membrane. A tracheobronchial membrane was found at autopsy in three cases, but was not identified before death in any patient. Judging from the above, the present case is an unusual diphtheria.

When acute exacerbation of chronic bronchitis due to common bacterias such as *Klebsiella pneumoniae*, elevation of inflammatory markers such as WBC, CRP and ESR are generally observed. But in the present case these markers were almost normal and the patient did not reveal systemic manifestation. We offer here two reasons why our case differed from the ordinary exacerbation of tracheobronchitis due to other common bacterias and *C. diphtheriae*. Here, the diphtheria was nontoxigenic, the bacteria did not invade the submucosal tissue (6) and there was no systemic manifestation, only local inflammation of trachea. This might be a distinct character of exacerbation of tracheobronchitis due to nontoxigenic *C. diphtheriae*.

The immunological effects of some macrolides have been reported (13). Recently at the 42th Japanese Congress of Chemotherapy Kobayashi et al (not published results) demonstrated that erythromycin inhibits the production of alginate which is responsible for the formation of biofilm in the mucoid morphotype of *Pseudomonas aeruginosa*. The production of alginate is ultimately responsible for the poor prognosis and high motality rates among patients with cystic fibrosis (14) as well as SBS. The prognosis of SBS however, especially that of DPB, is now good, since long-term, low dose erythromycin therapy (3, 4) has been proven to be excellent. Though antibiotic therapy seemed to be very successful in the present case, it is questionable whether both total intravenous administration dosage of cephazolin sodium 4g and oral erythromycin 600mg daily had a sufficient antibiotic effect on the bacteria. The reason why the pseudomembrane dominated the trachea and there were no significant lesions in the upper airway, we suppose, is that mucosal damage including insufficiency of mucociliary transport (3) associated with SBS was involved. In fact although she is free of lower airway symptoms, *Pseudomonas aeruginosa* and *Klebsiella ozaenae* were frequently recovered from her sputum at the outpatient clinic. As *Klebsiella ozaenae* was detected in her initial BALF and sputum coexisting *C. diphtheriae* we claim priority in reporting an association between exacerbation of tracheobronchitis and nontoxigenic *C. diphtherae*. Though there is no conclusive evidence, we suggest that colonization of nontoxigenic *C. diphtheriae mitis* was the a sole exacerbating factor and that low dose EM therapy was very successful in this case.

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