

Exudative Pharyngitis Possibly Due to *Corynebacterium pseudodiphtheriticum*, a New Challenge in The Differential Diagnosis of Diphtheria

Corynebacterium pseudodiphtheriticum has rarely been reported to cause disease in humans, despite its common presence in the flora of the upper respiratory tract. We report here a case of exudative pharyngitis with pseudomembrane possibly caused by *C. pseudodiphtheriticum* in a 4-year-old girl. The case initially triggered clinical and laboratory suspicion of diphtheria. Because *C. pseudodiphtheriticum* can be easily confused with *Corynebacterium diphtheriae* in Gram stain, clarification of its role in the pathogenesis of exudative pharyngitis in otherwise healthy persons is of public health importance. Simple and rapid screening tests to differentiate *C. pseudodiphtheriticum* from *C. diphtheriae* should be performed to prevent unnecessary concern in the community and unnecessary outbreak control measures.

Among the pathogenic nondiphtheria corynebacteria, *Corynebacterium pseudodiphtheriticum* has rarely been reported to cause disease in humans, despite its frequent presence in the flora of the upper respiratory tract (1,2). *C. pseudodiphtheriticum* was first isolated in humans by Von Hoffmann-Wellenhof from the throat of a patient in 1888 (2). The organism exhibits little pleomorphism. It appears as short gram-positive rods that often lie in parallel rows on smear preparation. We report here a case of exudative pharyngitis in a 4-year-old girl with a pseudomembrane possibly caused by *C. pseudodiphtheriticum*, which initially triggered suspicion of diphtheria, and provide a summary of previously published case reports.

Case Report

On November 6, 1994, a 4-year-old girl was admitted to the Emergency Room of St. Mary's Hospital in Rogers, Arkansas, with fever and generalized lymphadenopathy. Two other children in her home day care, including the patient's sibling, also had lymph node enlargement and fever. Her mother reported that the patient had not been immunized against any of the common childhood diseases but had an unremarkable medical history, with the exception of hand-foot-and-mouth disease at 3 years of age; she had never received antibiotics. Her developmental milestones were achieved on time. The family included the patient, her mother, father, and a 3-year-old sibling.

The patient's posterior pharynx was erythematous with swelling of the posterior

palate and with a thick grayish white membranous exudate adhering to the posterior wall of the pharynx. The pseudomembrane had almost completely detached and was gone, leaving behind ulcerated tissue. A discrete adenopathy in the neck and palpable nodes in the axillary, epitrochlear, and inguinal regions were observed.

The initial white blood cell count was 7,000 per ml, with 50% polymorphonuclear cells and 17% lymphocytes. A rapid screening test for group A streptococci and a Paul-Bunnell test for Epstein-Barr virus had negative results. Routine throat and nasopharyngeal swabs were collected and submitted to the hospital's clinical microbiology laboratory, where they were injected into blood agar and blood chocolate agar (special media for diphtheria culture were unavailable). From the throat swab, there was light growth of *Streptococcus pneumoniae* and light growth of gram-positive rods; a mixture of normal flora was also present. Gram-positive rods were also isolated from the nasopharyngeal swab. Subsequently, when subcultured on cystine-tellurite agar, these gram-positive rods grew as black colonies. Subcultures were then sent to the state laboratory, which confirmed them as *C. pseudodiphtheriticum*. After ambulatory treatment with cefprozil and erythromycin, the patient recovered in 4 days.

Investigation of Contacts

Because of its resemblance with *C. diphtheriae*, a *C. pseudodiphtheriticum* isolate was not immediately identified, and the case was initially

thought to be diphtheria. Consequently, 36 children and adults who had recently been in contact with the patient in day care, at the fitness center, or at the church were cultured for diphtheria. *C. diphtheriae* was not found, but *C. pseudodiphtheriticum* was found in the patient's 3-year-old sibling and in three additional persons: a 1-year-old girl and her 3-year-old brother, who lived in the same building as the patient and shared her day care, and a 54-year-old woman who attended the same church.

Microbiology and Molecular Characterization

The *C. pseudodiphtheriticum* isolate from the initial patient was forwarded to the Centers for Disease Control and Prevention (CDC), where it was assayed by phenotypic and genotypic methods. The identification was confirmed on the basis of growth characteristics and biochemical properties. The isolate was assayed by polymerase chain reaction (PCR), which detects 248 base pair fragments of the A subunit of the diphtheria toxin gene (3), and the result was negative. Additional PCR assays were performed with 12 sets of primers that cover the entire diphtheria toxin gene (*tox*) and diphtheria toxin regulatory element (*dtxR*); 560 base pairs of the *dtxR* were detected. However, the PCR results of its five prime and three prime ends were negative, indicating that the gene was nonfunctional.

Previous Case Reports¹

Since 1932, only 83 cases of disease possibly caused by *C. pseudodiphtheriticum* in humans have been reported. Until 1981, the only reported disease associated with this organism was endocarditis in the presence of anatomic abnormalities of the heart. Since then, this organism has been increasingly recognized as a pathogen of the lungs and bronchi, particularly in patients with underlying immunosuppressive conditions and preexisting pulmonary diseases and in patients undergoing endotracheal intubation.

Among reported cases, 19 were endocarditis (4-17); 61 involved infections of the lungs, trachea, or bronchi (18-32); one was a urinary tract infection (33); one involved a skin infection (34); and one was a vertebral discitis (35). All but three patients had underlying medical conditions,

including functional or anatomic abnormalities of the heart (N=27), lung and tracheobronchial diseases (N=28), endotracheal intubations (N=3), and immunosuppressive conditions including prolonged steroid use (N=6) and AIDS (N=4).

Most patients showed good clinical response to various antimicrobial drugs: penicillin, ampicillin, cefazolin, vancomycin, gentamicin, tobramycin, norfloxacin, and others. Nineteen (23%) deaths were reported overall. Information on sex was available for 80 cases; 54 (68%) were in males. Only five (6%) cases occurred in children <18 years of age; no cases were reported among children <5 years of age.

Since the early 1990s, diphtheria has returned in epidemic proportions in the former Soviet Union and is likely to be imported into other countries. Two cases of exudative upper respiratory tract infections with a pseudomembrane, in which the main organism isolated was *C. pseudodiphtheriticum*, have been reported. The first case was in a 54-year-old man with necrotizing tracheitis in 1991 (32). Santos et al. (36) reported isolation of *C. pseudodiphtheriticum* from a 32-year-old male Uzbek national who had a severe sore throat and dysphagia of 2 days duration. His tonsils were enlarged bilaterally, and a grayish-white exudate extended from the tonsil to the posterior pharyngeal wall. The uvula and soft palate were erythematous and edematous, and tender cervical lymphadenopathy was present. The presumptive clinical diagnosis in this patient was respiratory diphtheria.

Although the presence of a grayish pseudomembrane in the upper respiratory tract associated with isolation of *C. pseudodiphtheriticum* in these two cases and in the case we described is not proof that the isolated corynebacterium caused the pharyngitis or tracheitis, these accumulating case reports suggest that *C. pseudodiphtheriticum* may have played a pathogenic role.

The isolate from our patient was nontoxigenic by PCR. The diphtheria toxin is considered to be the main virulence factor of *C. diphtheriae* that causes the formation of the pseudomembrane in faucial diphtheria (37). Several possibilities could explain the presence of a pseudomembrane in infections with nontoxigenic corynebacterium strains. First, toxigenic and nontoxigenic colonies

¹A table listing all published case reports is available upon request from Dr. Hector Izurieta, Mail Stop A32, Centers for Disease Control and Prevention, 1600 Clifton Rd., Atlanta, GA 30333.

of the same species can coexist in a patient; this phenomenon has been reported in diphtheria (38). Multiple colonies would have to be tested to confirm this hypothesis in this case. Second, nontoxigenic forms of *C. diphtheriae* can produce invasive disease (39,40). It is possible that the symptoms in our patient were caused by a nontoxigenic *C. pseudodiphtheriticum* and that the pseudomembrane was simply an inflammatory exudate. This has been reported for *Arcanobacterium haemolyticum* (formerly *Corynebacterium haemolyticum*), which has also been associated with production of a grayish pharyngeal pseudomembrane (41,42). In 1960, Barksdale et al. reported a pseudomembrane in two laboratory workers contaminated with known nontoxigenic forms of *C. diphtheriae* (43). Third, we cannot exclude the possibility that the symptoms were caused by other organisms, including *S. pneumoniae*, which was found in the throat culture of our patient (29). However, this is unlikely because the growth of *S. pneumoniae* in our patient's throat culture was light, and the organism was not found in the nasopharyngeal swab. Furthermore, *S. pneumoniae* has not been reported to produce a pseudomembrane (44,45).

Because several other *Corynebacterium* spp. have been identified as potentially pathogenic for humans, routine screening for *C. diphtheriae* and other members of the *Corynebacterium* spp. in clinical samples of patients with respiratory infections should be encouraged (46). Full identification of gram-positive rods isolated from the respiratory tract, especially when they appear on original plates as the predominant organisms or copredominant with another species, should be carried out at the local, state, or reference level. Simple screening tests, such as negative cysteinase and positive pyrazinamidase, in addition to inability to ferment glucose, maltose, and sucrose quickly differentiate *C. pseudodiphtheriticum* from *C. diphtheriae*. These tests should be a part of improved training of laboratory personnel. Clinical and laboratory experience gained through this process will not only provide information about death rates for these organisms, but would be invaluable in preventing unnecessary concern in the community and the extraordinary measures needed to control dissemination of diphtheria.

Acknowledgments

We acknowledge Drs. Cynthia Whitman and Rosalind Carter, New York City Department of Health, and Dr. Robert S. Holzman, New York University Medical Center, for sharing information regarding a suspected case of diphtheria in New York; and Elizabeth Laborde, Alabama State Health Department's Laboratory, and Mary Beth Young, St. Mary's Hospital laboratory, Rogers, Arkansas, for sharing information regarding cultures for *C. pseudodiphtheriticum*.

Hector S. Izurieta,* Peter M. Strebel,* Thomas Youngblood,† Dannie G. Hollis,* and Tanja Popovic*

*Centers for Disease Control and Prevention, Atlanta, Georgia, USA; †Rogers Pediatric Clinic, Rogers, Arkansas, USA

References

1. Clarridge JE, Speigel CA. *Corynebacterium*, and miscellaneous irregular gram-positive rods, Erysipelothrix, and Gardnerella. In: Manual of clinical microbiology, 6th ed. Murray PR, Baron EJ, Pfaller MA, Tenover FC, Tenover RH, editors. Washington (DC): American Society for Microbiology, 1995:357-78.
2. Austrian R. *Streptococcus pneumoniae*. In: Gorbach SL, Bartlett JG, Blacklow NR, editors. Infectious Diseases. Philadelphia: W.B. Saunders Company, 1992:1412-15.
3. Mikhailovich VM, Melnikov VG, Mazurova IK, Wachsmuth IK, Wenger JD, Wharton M, et al. Application of PCR for detection of toxigenic *Corynebacterium diphtheriae* strains isolated during the Russian diphtheria epidemic, 1990 through 1994. J Clin Microbiol 1995;30:61-3.
4. Tow A, Wechsler HF. Diphtheroid bacillus as the cause of acute endocarditis. American Journal of Diseases of the Child 1932;44:156-61.
5. Olinger MG. Mixed infections in subacute bacterial endocarditis: report of two cases. Arch Intern Med 1948;81:334-41.
6. Morris A, Guild I. Endocarditis due to *Corynebacterium pseudodiphtheriticum*: five case reports, review, and antibiotic susceptibilities of nine strains. Reviews of Infectious Diseases 1991;13:887-92.
7. Johnson WD, Kaye D. Serious infections caused by diphtheroids. Ann NY Acad Sci 1970;174:568-76.
8. Rubler S, Harvey L, Avitabile A, Abenavoli T. Mitral valve obstruction in a case of bacterial endocarditis due to *Corynebacterium hofmannii*: echocardiographic diagnosis. New York State Journal of Medicine. 1982;82:1590-4.
9. Wilson ME, Shapiro DS. Native valve endocarditis due to *Corynebacterium pseudodiphtheriticum*. Clin Infect Dis 1992;15:1059-60.
10. Barrit DW, Gillespie WA. Subacute bacterial endocarditis. BMJ 1960;1:1235-9.
11. Blount JG. Bacterial endocarditis. Am J Med 1965;38:909-22.

12. Johnson WD, Cobbs CG, Arditi LI, Kaye D. Diphtheroid endocarditis after insertion of prosthetic heart valve: report of two cases. *JAMA* 1968;203:919-21.
13. Boyce JMH. A case of prosthetic valve endocarditis caused by *Corynebacterium hofmannii* and *Candida albicans*. *British Heart Journal* 1975;37:1195-7.
14. Wise JR, Bentall HH, Cleland WP, Goodwin JF, Hallidie-Smith KA, Oakley CM. Urgent aortic-valve replacement for acute aortic regurgitation due to infective endocarditis. *Lancet* 1971;2:115-21.
15. Leonard A, Raji L, Shapiro FL. Bacterial endocarditis in regularly dialyzed patients. *Kidney Int* 1973;4:407-22.
16. Lindner PS, Hardy DJ, Murphy TF. Endocarditis due to *Corynebacterium pseudodiphtheriticum*. *New York State Journal of Medicine* 1986;86:102-4.
17. Cauda R, Tamburrini E, Venture G, Ortona L. Effective vancomycin therapy for *Corynebacterium pseudodiphtheriticum* endocarditis (letter). *South Med J* 1987;80:1598.
18. Donaghy M, Cohen J. Pulmonary infection with *Corynebacterium hofmannii* complicating systemic lupus erythematosus. *J Infect Dis* 1983;147:962.
19. Miller RA, Rompalo A, Coyle MB. *Corynebacterium pseudodiphtheriticum* pneumonia in an immunologically intact host AIDS patients. *Lancet* 1992;340:114-5.
20. Cimolai N, Rogers P, Seear M. *Corynebacterium pseudodiphtheriticum* pneumonitis in a leukaemic child. *Thorax* 1992;47:838-9.
21. Roig P, López MM, Arriero JM, Cuadrado JM, Martín C. Neumonía por *Corynebacterium pseudodiphtheriticum* en paciente diagnosticado de infección por VIH. *An Med Interna* 1993;10:499-500.
22. Douat N, Labbe M, Glupczynski G. *Corynebacterium pseudodiphtheriticum* pneumonia in an anthracosilicotic man. *Clinical Microbiology Newsletter* 1989;11:189-90.
23. Andavolu RH, Venkita J, Lue Y, McLean T. Lung abscess involving *Corynebacterium pseudodiphtheriticum* in a patient with AIDS-related complex. *New York State Journal of Medicine* 1986;86:594-6.
24. Cohen Y, Force G, Grox I, Canzi AM, Lecleach L, Dreyfuss D. *Corynebacterium pseudodiphtheriticum* pulmonary infection in AIDS patients. *Lancet* 1992;340:114-5.
25. Yoshitomi Y, Higashiyama Y, Matsuda H, Mitsutake K, Miyazaki Y, Maesaki S, et al. Four cases of respiratory infections caused by *Corynebacterium pseudodiphtheriticum*. *Kansenshogaku Zasshi-Journal of the Japanese Association for Infectious Diseases* 1992;66:87-92.
26. Rikitomi N, Nagatake T, Matsumoto K, Watanabe K, Mbaki N. Lower respiratory tract infections due to non-diphtheria corynebacteria in 8 patients with underlying lung disease. *Tohoku J Exp Med* 1987;153:313-25.
27. Freeman JD, Smith HJ, Haines HG, Hellyar AG. Seven patients with respiratory infections due to *Corynebacterium pseudodiphtheriticum*. *Pathology* 1994;26:311-4.
28. Manzella JP, Kellogg JA, Parsey KS. *Corynebacterium pseudodiphtheriticum*: a respiratory tract pathogen in adults. *Clin Infect Dis* 1995;20:37-40.
29. Ahmed K, Kawakami K, Watanabe K, Mitsushima H, Nagatake T, Matsumoto K. *Corynebacterium pseudodiphtheriticum*: a respiratory tract pathogen. *Clin Infect Dis* 1995;20:41-6.
30. Craig TJ, Maguire FE, Wallace MR. Tracheobronchitis due to *Corynebacterium pseudodiphtheriticum*. *South Med J* 1991;84:504-6.
31. Williams EA, Green JD, Salazar S. Pneumonia caused by *Corynebacterium pseudodiphtheriticum*. *J Tenn Med Assoc* 1991;84:223-4.
32. Colt HG, Morris JF, Marston BJ, Sewell DL. Necrotizing tracheitis caused by *Corynebacterium pseudodiphtheriticum*: unique case and review. *Reviews of Infectious Diseases* 1991;13:73-6.
33. Nathan AW, Turner DR, Aubrey C, Cameron JS, Williams DG, Ogg CS, et al. *Corynebacterium hofmannii* infection after renal transplantation. *Clin Nephrol* 1982;17:315-8.
34. Lockwood BM, Wilson J. *Corynebacterium pseudodiphtheriticum* isolation. *Clinical Microbiology News* 1987;9:5-6.
35. Wright ED, Richards AJ, Edge AJ. Discitis caused by *Corynebacterium pseudodiphtheriticum* following ear, nose and throat surgery. *Br J Rheumatol* 1995;34:585-6.
36. Santos MR, Gandhi S, Vogler M, Hanna BA, Holzman RS. Suspected diphtheria in an Uzbek national: isolation of *C. pseudodiphtheriticum* resulted in a false positive presumptive diagnosis. *Clin Infect Dis* 1996;22:735.
37. Fontanarosa PB. Diphtheria in Russia a reminder of risk. *JAMA* 1995;273:1245.
38. Simmons LE, Abbot JD, Macaulay ME. Diphtheria carriers in Manchester: simultaneous infection with toxigenic and non-toxigenic mitis strains. *Lancet* 1980;2:304-5.
39. Tiley SM, Kociuba KR, Heron LG, Munro R. Infective endocarditis due to nontoxigenic *Corynebacterium diphtheriae*: a report of seven cases and review. *Clin Infect Dis* 1993;16:271-5.
40. Efstratiou A, Tiley SM, Sangrador A, Greenacre E, Cookson BD, Chen SCA, et al. Invasive disease caused by multiple clones of *Corynebacterium diphtheriae*. *Clin Infect Dis* 1993;17:136.
41. Kain KC, Noble MA, Barteluck RL, Tubbesing RH. *Arcanobacterium hemolyticum* infection: confused with scarlet fever and diphtheria. *J Emerg Med* 1991;9:33-5.
42. Robson JMB, Harrison M, Wing LW, Taylor R. Diphtheria: may be not! *Communicable Disease Intelligence* 1996;20:64-6.
43. Barksdale L, Garmise L, Horibata K. Virulence, toxigeny, and lysogeny in *Corynebacterium diphtheriae*. *Ann N Y Acad Sci* 1960;88:1093-108.
44. Austrian R. *Streptococcus pneumoniae*. In: Gorbach SL, Bartlett JG, Blacklow NR, editors. *Infectious Diseases*. Philadelphia: W.B. Saunders Company 1992:1412-15.