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Misidentification of Toxigenic *Corynebacterium diphtheriae* as a *Corynebacterium* Species with Low Virulence in a Child with Endocarditis

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A 6-year-old boy presented to a university hospital in Malaysia with infective endocarditis complicating cyanotic congenital heart disease. Blood cultures showed a gram-positive, aerobic, coryneform-like bacillus identified by the hospital laboratory as *Corynebacterium xerosis*, but a reference laboratory identified the organism as a toxigenic strain of *Corynebacterium diphtheriae*. The two laboratories concurred on all biochemical test results except for sucrose fermentation.

Corynebacterium diphtheriae infection causes localized inflammatory lesions of the upper respiratory tract or skin, with associated necrosis at distant sites (myocarditis and neuritis) attributable to the dissemination of diphtheria exotoxin. In rare cases, the organism can cause endocarditis (3, 6, 7, 9, 12–14), septic arthritis (1), and splenic abscess (2). Of the 55 cases of *C. diphtheriae* endocarditis that have been reported, 25 were in children. Since the advent of antibiotics, only two cases were due to toxigenic strains (3, 9). The previously reported pediatric cases (3, 6, 7, 9, 12–14) and this case are summarized in Table 1.

CASE REPORT

A 6-year-old boy with uncorrected cyanotic congenital heart disease was admitted to a university teaching hospital in Malaysia in April 1994 because of a 2-week-long fever. There was no recent sore throat, respiratory distress, chest pain, or skin infection. He had received three primary doses and one booster dose of diphtheria-tetanus toxoid vaccine within the first 2 years of life and no further doses. He had central cyanosis, finger clubbing, and a petechial rash on the face and the arms without splinter hemorrhages, Osler nodes, or Janeway lesions. There was a grade IV/VI pansystolic murmur loudest in the third and fourth intercostal spaces at the left sternal border. The liver edge was palpable 2 cm below the right costal margin. The spleen was palpable at the left costal margin. Transthoracic two-dimensional echocardiography showed a hypertrophic single ventricle, an anteriorly positioned aorta, a dilated right atrium, a normal mitral valve, a thickened tricuspid valve with one small vegetation, and a large, pedunculated vegetation over the aortic root. All six blood cultures obtained on the day of admission yielded gram-positive, nonmotile, aerobic bacilli which were identified as *Corynebacterium xerosis* by the hospital's Microbiology Laboratory. A diagnosis of nondiphtherial corynebacterium infective endocarditis was made, and the child was treated with intravenous penicillin and chloramphenicol for 6 weeks. He became afebrile after 4 days of treatment. Serial echocardiography showed gradual resolution of the vegetations on the tricuspid valve, but no diminution of those at the aortic root. Twenty weeks after discharge, he had regained his baseline state of health.

The *Corynebacterium* blood culture isolate was sent to the Provincial Public Health Laboratory in Toronto, Ontario, Canada, which identified the organism not as *C. xerosis* but as a toxigenic strain of *C. diphtheriae* biotype gravis, the organism recognized as the cause of acute diphtheria. The results of biochemical tests by standard methods (8) were as follows: catalase positive; nitrate reduction positive; urease negative; esculin hydrolysis negative; and fermentation of glucose, maltose, and glycogen but not sucrose. The toxigenic nature of the isolate was determined by the gel precipitin test described by Elek (11). Antimicrobial disk susceptibility tests by standard methods (17) revealed resistance to oxacillin but susceptibility to the following antimicrobial agents: penicillin G, vancomycin, erythromycin, clindamycin, chloramphenicol, tetracycline, ciprofloxacin, and gentamicin.

DISCUSSION

The following clinical features demonstrated by our patient were similar to the pediatric cases of *C. diphtheriae* endocarditis reported by Almklov and Hansen in 1950 (3) and Davidson et al. in 1976 (9): underlying structural heart disease, previous immunization against diphtheria toxin, multiple blood cultures positive for toxigenic strains of *C. diphtheriae*, lack of manifestations mediated by diphtheria toxin, satisfactory response to antibiotic therapy, and no evidence of concurrent nasopharyngeal or cutaneous diphtheria. As these cases demonstrate, immunized patients may have *C. diphtheriae* bacteremia and endocarditis in the absence of the characteristic, toxin-mediated, necrotizing lesions, because the invasive and toxigenic properties of *C. diphtheriae* are independent of each other (18).

The misidentification of the organism by the hospital's laboratory can be explained by an erroneously positive result of the sucrose fermentation test. The hospital and reference laboratories concurred on all other biochemical tests. In the admitting hospital, the positive result of the sucrose fermentation test caused *C. diphtheriae* to be ruled out and the organism to be identified as *C. xerosis*, a nondiphtheria corynebacterium

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TABLE 1. Features of toxigenic *C. diphtheriae* endocarditis in 11 children

Yr	Age (yr)	Gender[a]	Naso-pharyngeal diphtheria	Valve[b] involved	Outcome	Reference
1918	7	M	No	M	Died	13
1933	6	F	Yes	T	Died	6
1935	10	F	Yes	M	Died	7
1936	10	F	Yes	M	Died	14
1936	8	M	Yes	M	Died	14
1936	9	M	Yes	None	Died	14
1936	4	F	Yes	M	Died	14
1941	5	F	Yes	M	Died	12
1950	8	F	No	NS	Survived	3
1976	4	F	No	NS	Survived	9
1994	6	M	No	T, A	Survived	This work

[a] M, male; F, female.
[b] M, mitral; T, tricuspid; A, aortic; NS, not specified.

with relatively low virulence that is usually a cutaneous commensal but has been reported to cause infection in immunocompromised patients and those with indwelling mechanical devices (15). There are several possible explanations for the false-positive sucrose fermentation test: (i) overheating of the medium in the sucrose test leading to hydrolysis of sucrose to glucose and fructose (the resultant fermentation of glucose by the organism would be misinterpreted as fermentation of sucrose), (ii) inadvertent contamination of the *C. diphtheriae* inoculum with a sucrose-fermenting organism, (iii) misinterpretation of the test's pH indicator color. If the laboratory had used a known strain of *C. diphtheriae* as a positive control, the erroneous result with the sucrose fermentation test would have been detected. In addition, a negative result on a pyrazinamidase test (8) could have alerted the laboratory to the possibility that the isolate was *C. diphtheriae.*

There were only 12 cases of diphtheria reported in Malaysia in 1991 (10). The hospital's laboratory recorded no *C. diphtheriae* isolates from any sites in the preceding 6 years for which records were available. During that period, there were 119 blood culture isolates identified as nondiphtheria corynebacteria, 14 of which were identified as *C. xerosis*. Three of these isolates were obtained from an 11-year-old girl in whom a diagnosis of *C. xerosis* endocarditis was made (16). None of the previous *C. xerosis* isolates was sent to a reference laboratory, so it is possible that there have been several erroneous results with the sucrose fermentation test and that any number of isolates were actually *C. diphtheriae*. If that were the case, the prevalence of *C. diphtheriae* infections in the region served by the hospital would be greater than has been appreciated by the medical community.

The difficulty in accurately identifying *C. diphtheriae* is of concern because it raises the question of whether similar laboratory errors occur in other parts of the world. These potential errors are particularly significant in view of the dramatic increase in the number of cases of clinical diphtheria in the new independent states of the former Soviet Union (5) and of the reports of diphtheria among North Americans travelling there (4). Laboratory quality assurance programs should incorporate positive-control tests into all routine diagnostic methods, with special attention to proficiency in identifying *C. diphtheriae*, a pathogen often forgotten in industrialized and emerging nations.

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