Corynebacterium CDC group G native and prosthetic valve endocarditis

Adil Sattar,[1] Siegfried Yu,[2] Janak Koirala[3]

[1]Department of Internal Medicine, University of New Mexico School of Medicine, Albuquerque, NM; [2]Department of Internal Medicine, [3]Department of Infectious Diseases, Southern Illinois University School of Medicine, Springfield, IL, USA

Abstract

We report the first case of native and recurrent prosthetic valve endocarditis with *Corynebacterium* CDC group G, a rarely reported cause of infective endocarditis (IE). Previously, there have been only two cases reported for prosthetic valve IE caused by these organisms. A 69-year-old female with a known history of mitral valve regurgitation presented with a 3-day history of high-grade fever, pleuritic chest pain and cough. Echocardiography confirmed findings of mitral valve thickening consistent with endocarditis, which subsequently progressed to become large and mobile vegetations. Both sets of blood cultures taken on admission were positive for *Corynebacterium* CDC group G. Despite removal of a long-term venous access port, the patient's presumed source of line associated bacteremia, mitral valve replacement, and aggressive antibiotic therapy, the patient had recurrence of vegetations on the prosthetic valve. She underwent replacement of her prosthetic mitral valve in the subsequent 2 weeks, before she progressed to disseminated intravascular coagulation and expired. Although they are typically considered contaminants, corynebacteria, in the appropriate clinical setting, should be recognized, identified, and treated as potentially life-threatening infections, particularly in the case of line-associated bacteremias, and native and prosthetic valve endocarditis.

Introduction

Non-diphtheriae *Corynebacterium* species, more commonly known as diphtheroids, are aerobic, non-sporulating, gram-positive bacilli that are usually considered non-pathogenic components of normal skin flora and mucous membranes. Although these bacteria are commonly assumed to be contaminants, their ability to cause disease is being increasingly recognized. Over the last decade, there have been increasing reports on their pathogenic potential, particularly in bacteremia and endocarditis.[1-6] Previously, there were two cases reported for prosthetic valve only infective endocarditis (IE) with *Corynebacterium* CDC group G in 1983 and 1991.[7,8] In the current report, we describe the third case of a yet non-speciated *Corynebacterium* CDC group G endocarditis. Our is the first report of a native valve IE by these organisms with the previous reports involving prosthetic valves. We propose that this group should be recognized as an underdiagnosed and under-reported yet virulent pathogen of endocarditis.

Case Report

A 69-year-old woman presented to the emergency department with a 3-day history of high-grade fever, pleuritic right lower chest pain and cough. Physical examination revealed an elevated temperature of 38.8°C, bibasilar crackles, lower extremity edema and a grade 3 holosystolic apical murmur secondary to known mitral valve regurgitation. She also had a long-term venous access port for recurrent transfusion-dependent anemia, that had been in place for 3 years.

Laboratory examinations revealed hemoglobin 12.1 g/dL; white blood cell count, 15.1×10^3/µL; absolute neutrophil count 13.2×10^3/µL; and b-type natriuretic peptide 788 pg/mL.

Chest radiography revealed changes consistent with congestive heart failure. Electrocardiography showed a previously known left bundle branch pattern. Two out of two blood cultures drawn at the time of admission were positive for *Corynebacterium* CDC group G. Both specimens were also gram stain positive for gram positive rods. *Corynebacterium* CDC group G was identified using biochemical tests recommended by The Clinical and Laboratory Standards Institute (CLSI).

Transthoracic echocardiography demonstrated moderate mitral valve regurgitation, a thickened anterior mitral leaflet suggesting vegetations, and a severely elevated pulmonary artery systolic pressure of 84 mmHg. An echocardiogram done one year prior did not have this finding of mitral valve thickening. The patient was diagnosed with bacterial IE, secondary to *Corynebacterium* CDC group G, with involvement of the mitral valve. Susceptibilities for the organism were not performed. Due to a penicillin allergy, she was treated initially with intravenous vancomycin and clindamycin to complete a 6-week course. Her chronic implanted venous access port was removed, and she was discharged to an extended care facility to complete her antibiotic therapy. Three days after discharge she was readmitted due to sudden onset shortness of breath. In the Emergency Room she was hypoxic, and her white blood cell count was elevated to 18×10^3/µL. Intravenous vancomycin therapy was continued, and repeat transthoracic echocardiography showed severe mitral valve regurgitation, with a large and mobile vegetation on the mitral valve (Figure 1) worsened from the previous echocardiogram. For this reason, she underwent mitral valve replacement with a 27-mm Edwards-Carpentier pericardial valve and coronary artery bypass grafting surgery was done with a reverse saphenous vein graft to the distal right coronary artery. Pathology of her native mitral valve leaflet revealed endocarditis with fibrinopurulent exudate and granulation tissue and cultures were positive for diphtheroids. In the post-operative period she developed oliguric acute renal failure and respiratory failure requiring mechanical ventilation. Since the patient developed a urinary tract infection with vancomycin resistant enterococcus (VRE), vancomycin was discontinued and daptomycin therapy was started.

Patient continued to deteriorate with worsening congestive heart failure one week out of surgery. A transesophageal echocardiogram was done on day 17 of re-admission, which showed severe mitral valve regurgitation with a well-seeded mitral valve annular plane. Concomitant echo densities were observed on the mitral valve leaflets, strongly suspicious for

Correspondence: Adil Sattar, Department of Internal Medicine, University of New Mexico School of Medicine, MSC10-5550, 1 University of New Mexico, Albuquerque, NM 87131, USA.
Tel.: +1.505.272.4253
E-mail: adil.sattar@hotmail.com

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recurrent endocarditis of prosthetic valve. Antibiotic therapy was broadened with the addition of doxycycline, aztreonam, and anidulafungin to her regimen. Daptomycin was continued. The decision was to re-operate, and the porcine valve was replaced with a mechanical St. Jude's prosthesis (Figure 2). An intraoperative transesophageal echocardiogram confirmed a well-functioning prosthetic mitral valve. Pathology of her bioprosthetic mitral valve showed fibrous and fibro-inflammatory tissue consistent with endocarditis, but the cultures remained negative. The patient progressively deteriorated, with the development of limb ischemia and bleeding through her orifices and lines, and elevation of partial thromboplastin time and prothrombin time, consistent with disseminated intravascular coagulation. On the 21st re-admission day, she expired in multi-organ failure, and her family declined autopsy. Table 1 summarize the main events occurred to our patient from admission to death. All subsequent blood and tissue cultures performed during her admission were negative, except for the native mitral valve tissue culture positive for diphtheroids. We concluded, therefore, that the initial *Corynebacterium* CDC group G bacteremia was responsible for native and prosthetic valve endocarditis and that the subsequent cultures remained negative due to broad spectrum antibiotics. Review of records revealed two out of two prior blood cultures positive for diptheroids found during an admission for pneumonia 4 months prior to her current admission, which had been dismissed as contaminants, and not identified as a true source of infection. The potential for a line-associated bacteremia was not entertained at that time therefore identification was not done.

Discussion

Although endocarditis due to *Corynebacterium* CDC group G is quite rare, there have been increasing reports of nosocomial infections attributed to other corynebacteria, which include intravascular catheter-associated septicemia, native and prosthetic valve endocarditis, device-related infections, and postoperative surgical site infections. More commonly implicated diptheroids include the non-toxigenic *C. diptheriae, C. pseudodiphetriticum,* toxigenic *C. diphtheriae, C. striatum, C. jeikeium, C. xerosis, C. hemolyticum, C.minutissimum, and C.amycolatum.*[1,3] Diphtheroids cause approximately 0.2 to 0.4% of all cases of native valve endocarditis, and 9% of early and 4% of late prosthetic valve endocarditis.[5,9,10]

The previous reports of endocarditis with *Corynebacterium* CDC Group G involved prosthetic heart valves.[7,8] The present case is the first report, to our knowledge, of a native valve endocarditis with these organisms. In the case of endocarditis due to *Corynebacterium* CDC group G-2 reported by Austin and Hill in 1983,[4] the patient was a 40-year-old man who had rheumatic fever as a teenager and underwent mitral and aortic valve replacement with porcine valves at age 35. Six weeks after replacement of his porcine valves with Bjork-Shiley prosthetic valves, the patient developed a *flu-like* syndrome with high grade fever. Echocardiograms were negative, however, but he remained febrile with nine out of nine blood cultures positive for the organism. He was treated with vancomycin, tobramycin, and rifampin. He expired after 21 days of admission and autopsy revealed several small, friable vegetations on the mitral and aortic valve prostheses, with diptheroids identified on histologic examination.[7] Serra and Suma described the first case of *Corynebacterium* G-1 group endocarditis in 1991.[8] The bacterial strain in this case was isolated from the surgically removed heart valve. Since these initial reports, a study by Riegel *et al.*[11] found that 17 strains of *Corynebacterium* CDC group G-1 and G-2 could be grouped together by genetic means and should no longer be differentiated based on the ability to reduce nitrate as G-1 (nitrate reducer) or G-2 (nitrate negative), and therefore recommended the use of the term *CDC group G*.[11]

In our patient, the 2 out of 2 blood cultures positive for *Corynbacterium* CDC group G at the onset of her symptoms, her predisposing valvular heart condition, temperature >38.0°C, and echocardiographic findings demonstrating the development of large, mobile, and recurrent valvular vegetations, confirmed her initial diagnosis of definite IE by the Modified Duke's criteria.[12] The 2 prior blood cultures which were also positive for diphtheroids, not identified by the microbiology laboratory, suggest that she also had a chronic or intermittent line-associated bacteremia, given her chronic implanted venous access device, which we believe served as the nidus for the bacteremia. Notably, she was treated with a 14 day course of levofloxacin at that time for her pneumonia.

Since these organisms are seldom recognized for their pathogenic potential, the decision to identify diptheroids to the species level has been recommended in the following situations: when the bacteria are cultured from normally sterile sites such as blood or cerebrospinal fluid; if the bacteria are obtained in pure culture; if the bacteria appear in significant numbers on gram stains of clinical material; and if they are cultured in large numbers

Table 1. Major events occurred to our patient.

Day	Event	Treatment
0	Admitted and diagnosed with endocarditis	Vancomycin #0; clindamycin #0
5	Discharged to extended care facility for intravenous antibiotic therapy	Vancomycin #5; clindamycin #5
8	Re-admitted to hospital with hypoxia, fever, and worsening vegetations on echocardiogram	Vancomycin #8; clindamycin #8
9	Mitral valve replacement with bioprosthetic valve and coronary artery bypass grafting	
10	Post-op acute kidney injury and acute respiratory failure needing mechanical ventilation	Vancomycin #10; clindamycin #10
15	Vancomycin resistant enterococcus, urinary tract infection	Vancomycin discontinued; daptomycin #0
16	Worsening congestive heart failure	Daptomycin #1
19	Patient extubated	Daptomycin #4
25	Fever spikes and hypotension; transesophageal echocardiography showed worsening mitral regurgitation and recurrent vegetations of the bioprosthetic mitral valve	Daptomycin #10; doxycyclin #0; aztreonam #0; anidulafungin #0
26	Continued fever and sepsis; bioprosthetic mitral valve replaced by a St. Jude's mechanical mitral valve	Daptomycin #11; doxycyclin #1; aztreonam #1; anidulafungin #1
29	Limb ischemia, disseminated intravascular coagulation, multi-organ failure; patient expired	Daptomycin #14; doxycyclin #4; aztreonam #4; anidulafungin #4

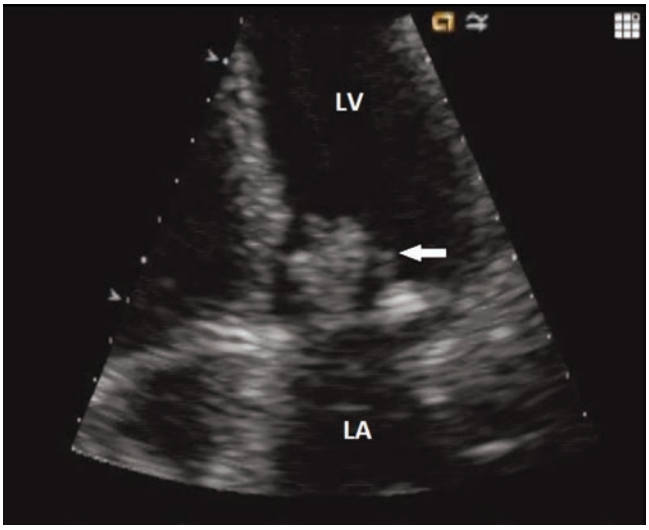

Figure 1. The repeat trans-thoracic echocardiogram is shown. The arrow points to the vegetation seen on the mitral valve. LV = Left ventricle. LA = Left atrium.

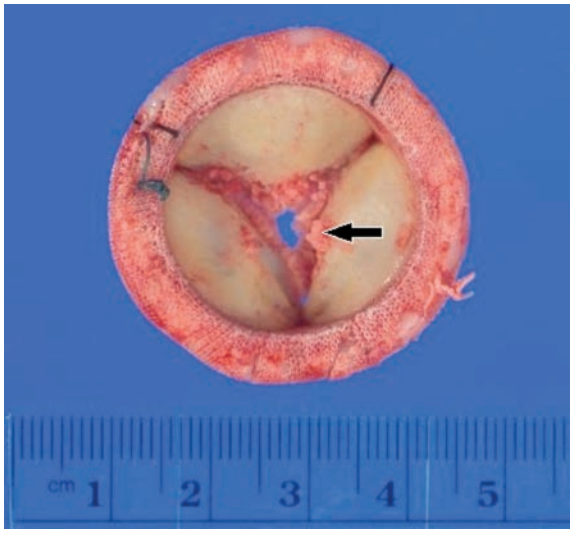

Figure 2. The initial Edwards-Carpentier bio-prosthetic valve is shown, with multiple vegetations scattered across the bio-prosthetic valve leaflets.

from the specimen.[4] Risk factors for *Corynebacterium* IE include preexisting cardiac disease, a prior history of IE, and the presence of prosthetic devices, particularly intravascular access catheters.[9] In their patient level analysis of 129 reported cases of *Corynebacterium* IE, Belmares *et al*.[1] found that over one quarter of these patients required valve replacement, and the mortality rate was a striking 43.4%, but they excluded the single reported case of *Corynebacterium* CDC Group G because the isolate was not identified to a species level.

A recent large prospective cohort study by the International Collaboration on Endocarditis - Prospective Cohort Study Investigators (ICE-PCS) found that the typical presentation of IE as described by Osler in the 19th century is now seldom encountered, and chronic rheumatic heart disease has become an uncommon predisposing factor.[13] Predisposing heart disease more frequently encountered includes degenerative valve disease of the elderly, mitral valve prolapse, intravenous drug misuse, preceding valve replacements, and vascular instrumentation.[14] This is accompanied by the emergence of previously undetected pathogens and multidrug resistant bacteria that challenge our conventional treatment regimens. Despite the advances in medical, surgical, and critical care interventions, IE remains a disease with significant morbidity and mortality which has not changed significantly in the past 25 years, and may even be increasing. Patients with health-care associated infections have emerged as a population at high risk for IE.[13-15]

The role of early surgery for infective endocarditis is becoming evident as more international research collaborations are established. A multi-disciplinary approach on deciding the timing of surgery for IE patients remains critical in better outcomes.

With the increasing proliferation of prosthetic medical devices, invasive procedures, chronic intravascular access devices, ports, and catheters, the frequency of nosocomial bloodstream infections caused by typically innocent bystanders, such as the corynebacteria, may be expected to increase. Corynebacteria are frequently cultured in polymicrobial infections, and they are usually contaminants in cultures collected with poor sterile technique or colonizers. When real disease caused by these organisms is suspected, however, clinician communication with the microbiology laboratory is essential to ensure the adequate identification of the organism, thus enabling the formulation of adequate therapy for the infection.

Conclusions

Corynebacterium CDC group G is a rarely reported cause of infection. However when present, it can cause disease which can be extremely difficult to eradicate before causing fatal illness with an established high rate of mortality. Disease caused by corynebacteria should be suspected particularly when multiple specimens are culture positive, and if it is present in large amounts. We have reported another rare case of *Corynebacterium* CDC group G native and prosthetic valve endocarditis, which serves as a reminder of the potential pathogenicity of these otherwise commonly dismissed contaminants. This also underscores the importance of communication between clinicians and the microbiology laboratory in order to prevent potentially fatal outcomes for our patients.

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