Case report

The patient was an 84-year-old female resident in a long-term care facility with end-stage renal disease requiring haemodialysis three times a week via a left subclavian haemodialysis catheter, and with atherosclerotic heart disease, hypertension and congestive heart failure. The patient was referred to our hospital from a dialysis centre with fever and hypotension. On physical examination, her blood pressure was 92/78 mmHg, her temperature was 39.8 °C and a new loud cardiac murmur localized in the mitral area was evident. No peripheral stigmata of endocarditis were present.

Initial blood work showed 17 800 leukocytes μl⁻¹ (84 % neutrophils, 16 % lymphocytes), and blood cultures performed at admission resulted in the growth of Gram-positive rods within 24 h in all four bottles. These were later identified as *Corynebacterium amycolatum* using the API Coryne database 2.0 (bioMérieux). Susceptibility by Etest gave the following MICs (μg ml⁻¹): penicillin, 16; ampicillin, 32; erythromycin, 16; levofloxacin, 16; rifampicin, 0.004; daptomycin, 0.19; linezolid, 0.38; and vancomycin, 0.5. Transthoracic echocardiography revealed normal functioning valves, without evidence of vegetation, thrombi or pericardial effusion. Transoesophageal echocardiography on hospital day 2 detected a small mobile echodensity attached to the mitral valve, consistent with a vegetation. Urine and sputum cultures remained negative for bacterial growth.

The patient initially received 1 g vancomycin intravenously after every haemodialysis and 1 g ceftriaxone intravenously every 12 h. Once *C. amycolatum* was identified on day 3, ceftriaxone was discontinued and oral rifampicin (300 mg every 12 h) was added. The patient refused to remove the haemodialysis catheter. Blood cultures from days 2–4 remained positive for *C. amycolatum*. On day 4, vancomycin was discontinued and daptomycin at a dose of 8 mg kg⁻¹ every 48 h was administered intravenously. Subsequent blood cultures from days 5–8 during antibiotic therapy remained negative for bacterial growth. The patient received a total of 6 weeks of daptomycin and 4 weeks of rifampicin treatment. Transoesophageal echocardiography carried out on completion of antibiotic therapy did not reveal any vegetation. The patient had a complete recovery with no elevated creatine phosphokinase levels or other adverse events.

Discussion

The taxonomy of coryneform bacteria has undergone significant modification since 1896 when Lehman and Neumann proposed that bacteria morphologically resembling the diphtheria bacillus be incorporated into the genus *Corynebacterium* (Lipsky et al., 1982). *C. amycolatum* is a normal inhabitant of human skin and was first described in 1988 as a Gram-positive, non-spore-forming, mycolic acid-free, aerobic or facultative anaerobic bacillus (Collins et al., 1988).

Physicians often disregard blood cultures that yield *Corynebacterium* species, as these organisms are usually classified as skin contaminants or ‘colonizers’. This is likely to be true when there is a single, isolated positive culture; however, multiple positive blood cultures, when performed in an appropriate aseptic manner, are more indicative of true bacteraemia. In a review, van Scoy et al. (1977) suggested that diphtheroids account for 10% of blood culture contaminants. Another study reported that *Corynebacterium* species accounted for 5% of the Gram-positive organisms that caused bacteraemia during trial VIII of the International Antimicrobial Therapy Cooperative Group of the European Organization for Research and Treatment of Cancer (Zinner, 1999).

A Medline search revealed 14 cases (De Miguel-Martinez et al., 1996; Berner et al., 1997; Vaneechoutte et al., 1998;
Corynebacterium laboratory setting. From 1987 to 1995, 11 new techniques, are not used in a routine clinical microbiology that reliably differentiate related species, such as mycolic acid-free Corynebacterium species. The majority of infections due to C. amycolatum were in either immunocompromised patients or patients with intravascular devices (De Miguel-Martinez et al., 1996; Berner et al., 1997; Vanechoutte et al., 1998; De Miguel et al., 1999; Oteo et al., 2001; Knox & Holmes, 2002; Chiu et al., 2005; Adderson et al., 2008). To date, they remain an uncommon cause of infective endocarditis (Knox & Holmes, 2002; Daniëls et al., 2003), even though other non-diphtherial corynebacteria, particularly Corynebacterium jeikeium, are becoming an increasingly common group of opportunistic pathogens. To the best of our knowledge, this is the first case report of C. amycolatum endocarditis from the USA treated with daptomycin and rifampicin.

Due to several modifications and the inclusion of new species into the genus Corynebacterium, it is becoming increasingly difficult to identify these organisms. Methods that reliably differentiate related species, such as mycolic acid chromatography, GLC and molecular amplification techniques, are not used in a routine clinical microbiology laboratory setting. From 1987 to 1995, 11 new Corynebacterium species were described (Funke et al., 1997). C. amycolatum has recently been included in the updated API Coryne database 2.0 (Wauters et al., 1998). The presence of only two reports of C. amycolatum causing endocarditis in the literature may be due to its misidentification, as other non-lipophilic fermentative Corynebacterium species, including Corynebacterium xerosis and Corynebacterium minutissimum, are associated with human disease (Funke et al., 1996a; Zinkernagel et al., 1996). Letek et al. (2006) described a molecular method for rapid identification of C. amycolatum from the closely related Corynebacterium striatum, C. minutissimum and C. xerosis, without the requirement for further molecular analysis, based on the use of different primers for amplification of the cell-division divIVA gene using conventional or real-time PCR (Letek et al., 2006). Again, these techniques are not performed routinely in clinical microbiology laboratories.

Published material provides useful schema for differentiating C. amycolatum, C. minutissimum and C. striatum using colony morphology, carbohydrate assimilation tests and sensitivity to amoxicillin and the vibriostatic compound O/129, in conjunction with the API Coryne and API 20NE systems. Antibiotic sensitivity patterns may support identification, with C. amycolatum and C. jeikeium generally resistant to multiple antibiotics (Renaud et al., 1998). In contrast, C. striatum, C. minutissimum and C. xerosis are generally sensitive to a wide range of antibiotics.

Sánchez Hernández et al. (2003) tested 58 strains of C. amycolatum (including 33 multidrug-resistant strains); they showed no resistance to teicoplanin or linezolid and 1 strain was resistant to quinupristin/dalfopristin. Goldstein et al. (2003) showed that 29/31 strains of Corynebacterium species, including C. jeikeium, C. amycolatum and Corynebacterium pseudodiphteriticum, were inhibited by ≤0.25 µg daptomycin ml⁻¹. The Clinical and Laboratory Standards Institute (CLSI, 2006a, b) does not report susceptibility criteria for Corynebacterium species and therefore susceptibility data generated in the microbiology laboratory should be interpreted with caution, as data linking MIC results to clinical outcomes are lacking.

C. amycolatum is quite sensitive to glycopeptide/lipopeptide antibiotics, as was the isolate presented in this report (Funke et al., 1996b; Sánchez Hernández et al., 2003). Thirteen of the fifteen patients with C. amycolatum infections for whom treatment data were available were given at least a glycopeptide antibiotic, as listed in Table 1. Because of the paucity of documented case reports, there is no consensus on the optimal treatment C. amycolatum endocarditis. Knox & Holmes (2002) successfully treated a case of endocarditis due to C. amycolatum with vancomycin and oral rifampicin for 16 months. In our case, we switched to daptomycin as our patient was on haemodialysis and was bacteraemic on vancomycin therapy for 4 days. Whilst daptomycin is only approved for bacteraemia and right-sided endocarditis caused by Staphylococcus aureus, the exquisite bactericidal nature and ease of administration of this agent prompted our switch in therapy. Her bacteraemia cleared after 24 h on daptomycin therapy and she had a favourable outcome after 6 weeks of daptomycin and 4 weeks of rifampicin.

In summary, C. amycolatum is classified as a fermentative, non-lipophilic, mycolic acid-free Corynebacterium species and is capable of causing serious human infections. C. amycolatum isolated in this and other reported cases of endocarditis was susceptible to vancomycin or daptomycin in the laboratory, and patients treated with these antimicrobial agents in combination with rifampicin had successful microbiological and clinical outcomes. The description of further cases treated with vancomycin and daptomycin, alone or in combination, may lead to more formal therapeutic guidelines. With the increase in newer identification schemes routinely performed in clinical laboratories, non-diphtherial Corynebacterium species are likely to be implicated in a growing number of infections.
Table 1. Infections due to *C. amycolatum*

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age/sex</th>
<th>Co-morbidity</th>
<th>Diagnosis</th>
<th>Associated IVD</th>
<th>Antibiotic susceptibility</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Miguel-Martinez et al.</td>
<td>75 years/F</td>
<td>Acute non-lymphocytic leukaemia, DM</td>
<td>Neutropenic septicemia</td>
<td>None</td>
<td>Teicoplanin, vancomycin, amikacin, netilmicin</td>
<td>Piperacillin/tazobactam, amikacin, teicoplanin</td>
<td>Survived</td>
</tr>
<tr>
<td>Berner et al. (1997)</td>
<td>2 days/M</td>
<td>Premature</td>
<td>Septic shock syndrome</td>
<td>None</td>
<td>Imipenem, vancomycin, erythromycin, clindamycin</td>
<td>Piperacillin, netilmicin, dopamine, dobutamine, norepinephrine</td>
<td>Died</td>
</tr>
<tr>
<td>Vaneecoutte et al. (1998)</td>
<td>42 years/F</td>
<td>ACD, SVC syndrome, recurrent ACD pocket infections</td>
<td>Cardioverter lead electrode infection</td>
<td>ACD</td>
<td>Vancomycin</td>
<td>Ampicillin, vancomycin, fluconazole and removal of ACD and electrode</td>
<td>Survived</td>
</tr>
<tr>
<td>Clarke et al. (1999)</td>
<td>63 years/M</td>
<td>HTN, OA</td>
<td>Septic arthritis</td>
<td>None</td>
<td>Teicoplanin, vancomycin, gentamicin, fusidic acid, doxycycline, ciprofloxacin</td>
<td>Flucloxacin, vancomycin, rifampicin, doxycycline</td>
<td>Survived</td>
</tr>
<tr>
<td>De Miguel et al. (1999)</td>
<td>75 years/F</td>
<td>DM, acute leukaemia</td>
<td>Neutropenic septicemia</td>
<td>None</td>
<td>No data</td>
<td>Ceftazidine, amikacin, teicoplanin</td>
<td>Survived</td>
</tr>
<tr>
<td>De Miguel et al. (1999)</td>
<td>53 years/F</td>
<td>Acute leukaemia</td>
<td>Neutropenic septicemia</td>
<td>None</td>
<td>No data</td>
<td>Piperacillin/tazobactam, amikacin, teicoplanin</td>
<td>Survived</td>
</tr>
<tr>
<td>Oteo et al. (2001)</td>
<td>70 years/M</td>
<td>Laryngeal carcinoma, chronic bronchitis, DM, DVT</td>
<td>Incarcerated umbilical hernia, RLL pneumonia</td>
<td>None</td>
<td>No data</td>
<td>Doxycycline, vancomycin, rifampicin</td>
<td>Survived</td>
</tr>
<tr>
<td>Oteo et al. (2001)</td>
<td>70 years/M</td>
<td>DM</td>
<td>Left hip fracture with ORIF, septicemia</td>
<td>None</td>
<td>Doxycycline, vancomycin</td>
<td>Vancomycin</td>
<td>Died</td>
</tr>
<tr>
<td>Knox &amp; Holmes (2002)</td>
<td>74 years/F</td>
<td>Adenocarcinoma of stomach</td>
<td>Empyema, haemothorax</td>
<td>CVC</td>
<td>Doxycycline, vancomycin</td>
<td>Vancomycin</td>
<td>Died</td>
</tr>
<tr>
<td>Daniëls et al. (2003)</td>
<td>88 years/M</td>
<td>LVH, AS, decubitus ulcer</td>
<td>Native aortic valve endocarditis</td>
<td>Right IJ HD catheter</td>
<td>No data</td>
<td>Vancomycin, rifampicin</td>
<td>Survived</td>
</tr>
<tr>
<td>Chiu et al. (2005)</td>
<td>65 years/F</td>
<td>ESRD, CAPD</td>
<td>Peritonitis</td>
<td>Tenckhoff catheter</td>
<td>No data</td>
<td>Cefazolin, ceftazidine, vancomycin</td>
<td>Survived</td>
</tr>
<tr>
<td>Adderson et al. (2008)</td>
<td>4 years/F</td>
<td>ALL, disseminated histoplasmosis, hyperglycemia</td>
<td>Neutropenic septicemia</td>
<td>CVC</td>
<td>No data</td>
<td>Vancomycin, meropenem</td>
<td>No data</td>
</tr>
<tr>
<td>Adderson et al. (2008)</td>
<td>9 years/M</td>
<td>ALL, SCT, GVHD</td>
<td>Neutropenic septicemia</td>
<td>CVC</td>
<td>No data</td>
<td>Vancomycin, ceftazime, removal of CVC</td>
<td>No data</td>
</tr>
<tr>
<td>Present case</td>
<td>84 years/F</td>
<td>ESRD, ASH, HTN, CHF</td>
<td>Native mitral valve endocarditis</td>
<td>Left subclavian HD catheter</td>
<td>Vancomycin, linezolid, daptomycin, rifampicin</td>
<td>Vancomycin, daptomycin, rifampicin</td>
<td>Survived</td>
</tr>
</tbody>
</table>

ACD, Automated cardioverter defibrillator; ALL, acute lymphocytic leukaemia; ANCA, anti-neutrophilic cytoplasmic antibody; AS, aortic stenosis; ASHD, atherosclerotic heart disease; CAPD, continuous peritoneal ambulatory peritoneal dialysis; CHF, congestive heart failure; CVC, central venous catheter; DM, diabetes mellitus; DVT, deep venous syndrome; ESRD, end-stage renal disease; F, female; GVHD, graft-versus-host disease; HD, haemodialysis; HTN, hypertension; IJ, internal jugular; IVD, intravascular device; LVH, left ventricular hypertrophy; M, male; OA, osteoarthritis; ORIF, open reduction and internal fixation; RLL, right lower lobe; SCT, stem-cell transplant; SVC, superior vena cava.
The increasing number of immunocompromised patients and the burgeoning use of intravascular access devices have also contributed to this phenomenon.

References


