Nocardia cyriacigeorgica: a case of endocarditis with disseminated soft-tissue infection

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Nocardia cyriacigeorgica is a common environmental organism. It has been isolated from clinical samples in Europe, Asia and North America, predominantly from respiratory samples but also from samples from several other sites. We present a case report of an 85-year-old female patient in the UK who was found to have a multi-focal soft-tissue infection from which N. cyriacigeorgica was isolated. She had a background history of chronic obstructive pulmonary disease and corticosteroid use for polymyalgia rheumatica. During the course of her treatment echocardiography showed the presence of a mobile heart mass attached to a valve leaflet, a major Dukes criterion for endocarditis. We suggest that in cases of disseminated Nocardia infection, endocarditis should be tested for, particularly in cases failing to respond to treatment. We also review previous reports of both N. cyriacigeorgica infection, and of endocarditis due to Nocardia species and related genera.

Introduction

Nocardia cyriacigeorgica (initially described as ‘Nocardia cyriacigeorgii’) was first reported in 2001 from a patient with chronic bronchitis (Yassin et al., 2001). Nocardia species are branching Gram-positive bacilli belonging to the family Nocardiaceae, together with the genus Rhodococcus, within the suborder Corynebacterineae of the Actinobacteria (Stackebrandt et al., 1997). They are related to the families Mycobacteriaceae, Gordoniaceae, Tsukamurellaceae and Dietziaceae. The Nocardia cell wall contains tuberculostearic acids, like Mycobacteria, but also short chain mycopic acids (Brown-Elliott et al., 2006). They are common environmental organisms worldwide, although some species show some geographical variance in prevalence (Brown-Elliott et al., 2006). The introduction of molecular typing methods led to the specification of the Nocardia asteroides complex between defined antimicrobial-susceptibility patterns, with for example type I susceptibility patterns corresponding to Nocardia abscessus (Brown-Elliott et al., 2006). Isolates with type VI patterns were shown to be N. cyriacigeorgica (Conville & Witebsky, 2007), although N. cyriacigeorgica may be susceptible to ampicillin (Brown-Elliott et al., 2006) and ciprofloxacin (Barnaud et al., 2005).

Reports of the relative frequency of isolation of N. cyriacigeorgica among clinically significant Nocardia show similar rates in both Europe and Asia. In Belgium, N. cyriacigeorgica accounts for 15% of Nocardia isolates, third after Nocardia farcinica and Nocardia nova (Wauters et al., 2005). In Spain, it accounts for 22% of isolates, equal second with N. abscessus, after N. farcinica (Muñoz et al., 2007). In Japan 10% of Nocardia are N. cyriacigeorgica, the fourth most common species after N. farcinica, N. asteroides sensu stricto and N. nova (Kageyama et al., 2004); while in Thailand N. cyriacigeorgica is the third most frequently isolated Nocardia after N. farcinica and Nocardia beijingensis, comprising 14% of isolates (Poonwan et al., 2005). In the southern USA N. asteroides drug type VI is the most frequently reported Nocardia (Brown-Elliott et al., 2006), while N. cyriacigeorgica infection has also been reported from Turkey (Akca et al., 2008; Alp et al., 2006), Greece (Maraki et al., 2006), France (Barnaud et al., 2005), Canada (Elsayed et al., 2006), the USA (Schlaberg et al., 2008), India (Lalitha et al., 2007) and Germany (Fux et al., 2003), suggesting a worldwide distribution of potentially pathogenic strains.

We present a case of possible endocarditis associated with disseminated skin and soft-tissue infection caused by N. cyriacigeorgica, and review the reported cases of endocarditis due to Nocardia species and the related genera Rhodococcus, Dietzio, Tsukamurella and Gordonia.

Case report

An 85-year-old female with a past history of ischaemic heart disease, chronic obstructive pulmonary disease and polymyalgia rheumatica was admitted in March 2008 to a North Yorkshire district hospital following multiple falls...
and abdominal pain. Her polymyalgia rheumatica had been diagnosed within the previous 6 months, following which she had had a reducing course of oral prednisolone. On presentation she was tachycardic, hypotensive and hypoxic, with bilateral crepitations and reduced air entry at the right lung base. Her white cell count was $23 \times 10^9$ cells $l^{-1}$ (normal range 3.6–11.0 $\times 10^9$ cells $l^{-1}$), her C-reactive protein level was 289 mg $l^{-1}$ (normal range 0–10 mg $l^{-1}$) and a chest X-ray showed consolidation of the left lower lobe. In addition to her respiratory symptoms she had left iliac fossa tenderness with a sinus discharging yellow fluid in the right iliac fossa. A soft fluctuant swelling was noted on her left flank. Her heart sounds were normal with no murmurs detected. She was on oral steroids at the time of admission, and was taking clarithromycin following a previous course of fluoroquinolone taken whilst in the community. A diagnosis of pneumonia was made, and she was commenced on intravenous cefuroxime and metronidazole (changed after 5 days to oral amoxicillin). At the same time hydrocortisone was prescribed. Fluid from the sinus was processed according to a local standard operating procedure (SOP), based on the relevant national SOP (HPA, 2006). Cultures on blood agar (aerobic incubation at 36 °C for 48 h), cysteine lactose electrolyte deficient agar (CLED) (aerobic incubation at 36 °C for 24 h), neomycin-fastidious anaerobe agar (neoFAA) and vancomycin/nalidixic acid-fastidious anaerobe agar (vnFAA) (both anaerobic incubation at 36 °C for 48 h) all yielded no growth. She was subsequently diagnosed with a hospital-acquired pneumonia when her condition deteriorated after 1 week in hospital, and was treated with intravenous piperacillin/tazobactam.

Two weeks after admission a 3 cm abscess was noted on her right forearm. This was incised and drained, and 10 ml pus was expressed. The following day vancomycin was added to her therapy to ensure empirical meticillin-resistant *Staphylococcus aureus* cover, and the piperacillin/tazobactam treatment was switched to imipenem as she remained short of breath and tachycardic. Pus samples were processed according to a local SOP based on the national SOP (HPA, 2008). No growth was recovered from the pus sample on blood agar (48 h) or CLED (24 h), or on neoFAA or vnFAA (5 days), and so vancomycin was stopped after 3 days, with the imipenem being stopped 3 days later.

Four days after drainage of the forearm abscess a fluctuant swelling of the left thigh was noted. An earlier ultrasound scan arranged by her general practitioner had shown an extensive tear of the rectus femoris. One week later a repeat scan demonstrated the presence of a large loculated abscess involving much of the anterior compartment of the thigh. Aspiration was performed and samples sent to the microbiology laboratory, where they were processed according to the local SOP. No antibiotics were prescribed as the abscess had been drained, but an echocardiogram was recommended. During the next 3 days further swellings were noted on the anterior chest wall and the right forearm. She again showed evidence of systemic sepsis, and vancomycin and imipenem therapy was given for 24 h.

Samples from the thigh abscess yielded Gram-positive bacilli on blood agar after 48 h of aerobic culture. The patient was restarted on vancomycin treatment, which was then changed to piperacillin/tazobactam after 3 days, before being changed to oral doxycycline. The organism was initially identified as a *Rhodococcus* species using an API Coryne test strip (bioMérieux) ($P=94.1\%$, $T=1.0$), but this identification method is known to be less reliable for rhodococci and related genera (Almuzara et al., 2006) the isolate was sent to the Centre for Infections at Colindale, London, for confirmation of both identity and antibiotic susceptibilities. Partial 16S rRNA gene sequencing (Bosshard et al., 2003) identified the isolate as *N. cyriacigeorgica*. The organism was reported to be susceptible to tetracycline, erythromycin, gentamicin and imipenem, but resistant to penicillin, ciprofloxacin, teicoplanin, vancomycin, rifampicin and fusidic acid. Pus from the anterior chest wall abscess also grew *N. cyriacigeorgica*. Over this period the patient had a fluctuant clinical condition, having intermittent periods of haemodynamic instability associated with pyrexia. Her white cell count and C-reactive protein level remained persistently elevated. A trans-thoracic echocardiogram demonstrated a thickening of a mitral valve leaflet with a small mobile mass on the apical four-chamber view, suggestive of endocarditis. The patient died 56 days after admission, 2 days after this mass was identified. There was no post-mortem examination, the cause of death being given as infective endocarditis on the death certificate.

### Discussion

We have reported here a case of possible endocarditis due to *N. cyriacigeorgica*. The patient had a major Dukes criterion (Baddour et al., 2005) (echocardiographic lesions) and multiple abscesses, which were felt to be consistent with a possible cardiac source (hence the recommendation for echocardiography during the admission). No other bacterial species were isolated from the lesions to suggest a possible mixed infection, and no organisms were ever recovered from blood culture. Only two blood cultures were received from the clinical team during the admission, both before the possibility of endocarditis was raised, and so they were only incubated for 7 days (Becton Dickinson Bactec 9240 automated blood culture system); four sets of cultures received in the previous 3 months were also negative after 7 days. The use of steroids over the course of several months may have masked the presence of minor Dukes criteria for endocarditis. The negative culture results from the initial iliac fossa sinus culture could have been due to insufficient culture time (over 48 h could have been necessary), and from the forearm abscess sample due to the preceding antimicrobial treatment. *N. cyriacigeorgica* has been described from cases of septicaemia (Elsayed et al., 2006), brain abscess (Alp et al., 2006; Barnaud et al., 2005; Fux et al., 2003), pleural empyema (Maraki et al., 2006),...
pulmonary infection (Akcaglar et al., 2008; Kageyama et al., 2005; Schlaberg et al., 2008) and keratitis (Lalitha et al., 2007). Many of these infections occur against a background of immunosuppression, for example chronic lymphocytic leukaemia (Elsayed et al., 2006), follicular non-Hodgkin’s lymphoma (Elsayed et al., 2006), human immunodeficiency virus infection (Barnaud et al., 2005; Kageyama et al., 2005) or corticosteroid therapy (as in this case) (Akcaglar et al., 2008; Kageyama et al., 2005; Maraki et al., 2006; Muñoz et al., 2007). Pulmonary infection has been reported in association with a number of predisposing lung conditions (Kageyama et al., 2005; Muñoz et al., 2007), including cancer, tuberculosis and bronchiectasis.

**Nocardia endocarditis**

*Nocardia* spp. are a rare cause of endocarditis (Brouqui & Raoult, 2001); 16 cases of endocarditis with *Nocardia* isolates have been described in the literature since 1970, and are shown in Table 1. Molecular testing of suspected cases of endocarditis showed 1 of the 22 positive cases to be caused by a *Nocardia* species (*Nocardia paucivorans* (Breitkopf et al., 2005), while a case series of endocarditis in renal transplant recipients reported 1 of 12 cases identified was caused by a *Nocardia* species (*N. asteroides*) (Bishara et al., 1999). *Nocardia* endocarditis has a high mortality, with 41% of cases (7 of 17 including this report) resulting in death. Nine cases (53%) were associated with prosthetic valves, either with the valve itself (Ayral et al., 1989; Chedid et al., 2007; Daikos et al., 2003; Falk et al., 1979; Vlachakis et al., 1973) or with infection at the site of valve surgery (Allevato et al., 1985; Eigel et al., 1988; Erlt et al., 1987). Several patients underwent surgery to replace a native valve (Antony et al., 2006; Chain et al., 2007; Lazo Torres et al., 2004; Watson et al., 2001) or prosthetic valve (Eigel et al., 1988; Erlt et al., 1987); in each case a successful outcome was reported in combination with antibiotic therapy. Valve replacement has been successful after the infection relapsed following antibiotic therapy (Eigel et al., 1988). Successful conservative management with antibiotic therapy alone has been reported (Antonovich et al., 2004; Chedid et al., 2007; Daikos et al., 2003). All but two of the successful treatments involved use of an aminoglycoside after *Nocardia* was identified as the infective agent (Ayral et al., 1989; Chedid et al., 2007; Chain et al., 2007; Daikos et al., 2003; Lazo Torres et al., 2004; Watson et al., 2001; Daikos et al., 2003; Eigel et al., 1988), with only one (Ayral et al., 1989) not combining a carbapenem with the aminoglycoside, and one (Antony et al., 2006) using a carbapenem but not an aminoglycoside. Only one (Eigel et al., 1988) did not complete treatment with co-trimoxazole. The remaining case (Antonovich et al., 2004) was treated with co-trimoxazole alone. Infection of an aortic aneurysm not associated with prosthetic materials has also been reported (Gates et al., 2006).

*N. cyriacigeorgica* should be susceptible to imipenem (Brown-Elliott et al., 2006), which had been an intermit-
<table>
<thead>
<tr>
<th>Patient age (years)/sex</th>
<th>Isolate (as reported)</th>
<th>Site</th>
<th>Culture</th>
<th>Antibiotic following isolation</th>
<th>Surgery</th>
<th>Outcome</th>
<th>Reference</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
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<td>Aminoglycoside</td>
<td>Carbapenem</td>
<td>Co-trimoxazole</td>
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<td>Yes</td>
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<td>IMI</td>
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<td>IMI</td>
<td>Yes</td>
<td>AVR</td>
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<td>IMI</td>
<td>Yes</td>
<td>MVR</td>
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<td>No</td>
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<td>AMI</td>
<td>No</td>
<td>No</td>
<td>Died</td>
</tr>
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</table>

AMI, Amikacin; AVR, aortic valve replacement; F, female; GEN, gentamicin; IMI, imipenem; M, male; MER, meropenem; MVR, mitral valve replacement; NA, not applicable; NAV, native aortic valve; NMV, native mitral valve; NTV, native tricuspid valve; PAV, prosthetic aortic valve.
term central venous catheters. A successful outcome was achieved using amoxicillin and netilmicin followed by ceftiraxone without valve replacement (Lesens et al., 2000); the second case was unsuccessfully treated (Verma et al., 2006).

Summary

A review of these organisms is complicated by taxonomic changes both within species, for example within the N. asteroides complex (Brown-Elliott et al., 2006), and between genera, for example Corynebacterium equi changed to Rhodococcus equi (Prescott, 1991), and reversals of previous changes, for example the incorporation of Gordonia into Rhodococcus before a divergence again to Gordonia (Prescott, 1991; Stackebrandt et al., 1997). Misidentification of these isolates is also common, for example N. cyriacigeorgica identified as a Rhodococcus species (this report), Tsukamurella as Mycobacterium (Alcaide et al., 2004) or Nocardia (Sheridan et al., 2003), Rhodococcus as Corynebacterium (Tuon et al., 2007), or Gordonia as Nocardia or Rhodococcus (Blaschke et al., 2007). For this reason this discussion has been limited to those cases where a bacterial isolate was reported, rather than histological reports of ‘Nocardia’-like organisms (Dhawan et al., 1998). Other morphologically similar organisms (loosely classified as aerobic actinomycetes) may also cause endocarditis, for example Oerskovia (Ellerbroek et al., 1998) and Rothia (Ricaurte et al., 2001) species, but are more distantly related to the Corynebacterineae (Stackebrandt et al., 1997). The changing taxonomies make the continued reporting of cases with the best possible identification important.

N. cyriacigeorgica has been described as ‘an emerging pathogen in the United States’ (Schlaberg et al., 2008), but might be better considered as ‘a newly named but long-recognised agent of human disease’ (Convil & Witebsky, 2007). We add this case report to the growing literature to help characterize the clinical spectrum of disease associated with N. cyriacigeorgica with the increased discrimination now available for the identification of Nocardia species. We believe this is the first report of endocarditis associated with N. cyriacigeorgica as a named species in the English literature, and reinforce the suggestion that the possibility of endocarditis cannot be excluded in patients with disseminated Nocardia infection.

Acknowledgements

We thank the Microbial Identification Services Unit of the Health Protection Agency’s Centre for Infections at Colindale, London, for the partial 16S rRNA gene sequencing.

References


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