Case Report

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 cyriacigeorgici*') 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 mycolic 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 (Akcaglar *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*, *Dietzia*, *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

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Abbreviation: SOP, standard operating procedure.

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 23×10^9 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 completed course of flucloxacillin 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 stopped3 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 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 as 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 sample 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; Ertl *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; Ertl *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 intermittent component of the antibiotic therapy received by our patient since early in her admission. Combination amikacin and ceftriaxone therapy followed by a long course of ceftriaxone alone has been successful in treating pulmonary *N. cyriacigeorgica* infection (Alp *et al.*, 2006), although the same combination was unsuccessful in treating a pleural empyema (Maraki *et al.*, 2006), as was imipenem in pulmonary infection (Akcaglar *et al.*, 2008). Combination imipenem, amikacin and ciprofloxacin, followed by co-trimoxazole and amoxicillin, has been used to successfully treat a brain abscess (Barnaud *et al.*, 2005), while combination meropenem and co-trimoxazole has been used in disseminated infection (Elsayed *et al.*, 2006).

Rhodococcus endocarditis

Endocarditis due to *Rhodococcus* has been reported rarely. Maltez *et al.* (1996) reported a case of mitral valve endocarditis in an human immunodeficiency virus positive patient. McNeil & Brown (1992) reported that 1 of their 107 clinical isolates was from a heart valve, while Torres-Tortosa *et al.* (2003) reported 1 isolate from the heart (otherwise unspecified) in their series of 67 patients. Bacteraemia has been reported more frequently, but in the few cases where echocardiography has been reported (Alric *et al.*, 2002; Gabriels *et al.*, 2006; Kedlaya *et al.*, 2001; Tuon *et al.*, 2007) the results have not indicated endocarditis.

Dietzia endocarditis

No cases of endocarditis have been reported due to *Dietzia* species, although bacteraemia (Bemer-Melchior *et al.*, 1999), intra-vascular infection (Reyes *et al.*, 2006) and infection of prosthetic material (Pidoux *et al.*, 2001) have all been reported due to *Dietzia maris*.

Tsukemurella endocarditis

A single case of infection of prosthetic cardiac material due to *Tsukamurella* was identified in the literature: an infection of an implanted cardioverter-defibrillator (Almehmi *et al.*, 2004). *Tsukamurella* was isolated from lead tip after removal of the device, and the patient was successfully treated with vancomycin and ciprofloxacin. Bacteraemia has been reported more frequently, often in association with central venous catheters (Bouza *et al.*, 2009; Chong *et al.*, 1997; Jones *et al.*, 1994; Schwartz *et al.*, 2002; Shapiro *et al.*, 1992; Sheridan *et al.*, 2003), but no cases of valve infection.

Gordonia endocarditis

Two cases of endocarditis due to *Gordonia* species have been reported: one due to *Gordonia polyisoprenivorans* (Verma *et al.*, 2006) and one that appeared related to *Gordonia sputi* (Lesens *et al.*, 2000). Both cases involved native valves, either the aortic (Verma *et al.*, 2006) or mitral (Lesens *et al.*, 2000), and were associated with long-

Table 1. Reported cases of endocarditis involving *Nocardia* isolates

Patient age (years)/ sex	Isolate (as reported)	Site	Culture			Antibiotic following isolation			Surgery	Outcome	Reference
			Blood	Valve	Other	Amino-glycoside	Carbapenem	Co-trimoxazole			
40/M	*Nocardia* spp.	PAV	Yes			GEN + AMI	IMI	Yes		Survived >5 years	Chedid *et al.* (2007)
51/M	*Nocardia* spp.	NAV & NTV	Yes			AMI	IMI	Yes	AVR	Survived >6 months	Chain *et al.* (2007)
53/F	*Nocardia* spp.	NMV		Yes		AMI	IMI	Yes	MVR	Survived	Lazo Torres *et al.* (2004)
34/F	*N. asteroides*	NAV & NMV				NA – post-mortem diagnosis				Died	Leonard *et al.* (1973)
34/F	*N. asteroides*	PMV			Cutaneous					Died	Vlachakis *et al.* (1973)
39/M	*N. asteroides*	NAV	Yes	Yes	Cutaneous	AMI	MER	Yes	AVR	Survived >18 months	Watson *et al.* (2001)
61/F	*N. asteroides*	PAV		Yes	Cutaneous	AMI	IMI	Yes		Survived >18 months	Daikos *et al.* (2003)
62/M	*N. asteroides* biovar A1	NAV			Cutaneous		IMI			Died	Niehues *et al.* (1996)
64/F	*N. asteroides*	PAV		Yes		NA – post-mortem identification				Died	Falk *et al.* (1979)
74/F	*N. asteroides*	NMV	Yes	Yes			IMI	Yes	MVR	Survived >1 year	Antony *et al.* (2006)
83/F	*N. asteroides*	NMV		Yes	Cutaneous			Yes		Survived	Antonovich *et al.* (2004)
68/M	*N. asteroides*	PAV			Hepatic artery	AMI		Yes		Survived	Ayral *et al.* (1989)
53/M	*N. asteroides*	Aneurysm associated with PAV	Yes	Yes						Died	Allevato *et al.* (1985)
61/M	*N. asteroides*	Aneurysm associated with PAV	Yes			AMI	IMI		AVR	Survived >3 years	Eigel *et al.* (1988)
61/M	*N. asteroides* biovar B (N. farcinica)	Aneurysm associated with PAV	Yes	Yes		AMI	IMI	Yes	AVR	Survived	Ertl *et al.* (1987)
65/M	*N. asteroides*	Aneurysm associated with PAV	Yes		Sternal osteomyelitis					Died	Eigel *et al.* (1988)
85/F	*N. cyriacigeorgica*	NMV			Cutaneous	AMI	IMI			Died	This report

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 ceftriaxone 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 *Gordona* 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' (Conville & 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.

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