

Brief Report

Nocardiosis in renal transplant recipients in Kuwait

M. R. N. Nampoory¹, Z. U. Khan², K. V. Johny¹, J. Nessim¹, R. K. Gupta¹, I. Al-Muzairai¹, M. Samhan³ and T. D. Chugh²

Departments of ¹Medicine, ²Microbiology and ³Surgery, Faculty of Medicine, Kuwait University and Mubarak Al-Kabeer Hospital, Ministry of Public Health, Kuwait

Abstract

Background. Nocardiosis has emerged as an important bacterial disease among renal transplant recipients, leading to considerable morbidity and mortality. Apart from the increasing problem of resistance in pathogenic nocardiae, the spectrum of species causing disease has enlarged in recent years. There are no published reports on nocardiosis from Middle-East countries.

Methods. A retrospective review of case records of 513 renal transplant recipients between January 1989 and January 1995 was done in the transplant unit of our hospital. Information was collected on clinical details, type of donor, immunosuppressive therapy, prophylaxis, and outcome. Isolation of *Nocardia* species from appropriate clinical specimens was the sole criterion for diagnosis.

Results. Nocardiosis was diagnosed in six recipients with a disease incidence of 1.2%. Four patients had received unrelated kidneys. Co-morbid conditions were diabetes mellitus (3), viral hepatitis (2) and neutropenia (1). Clinical manifestations included deep-seated skin abscesses and pulmonary disease in three each. Cerebral abscess and meningitis were found in two patients with pulmonary disease. Pathogens were *Nocardia asteroides* in four and *N. otiti discaviarum* and *N. farcinica* in one each. In contrast to *in vitro* susceptibility results, clinical response was different in that five patients who received trimethoprim-sulphamethoxazole (TMP-SMX) alone (2) or in combination with cefuroxime (3) responded well.

Conclusion. The study stresses a high index of suspicion for nocardiosis in susceptible hosts who present with cutaneous abscess, pulmonary infiltrative lesions, and cerebral manifestations. TMP-SMX in combination with cefuroxime seems to be a highly effective therapy. It does not appear mandatory to reduce or discontinue immunosuppressive therapy during treatment of nocardiosis.

Key words: nocardiosis; renal transplant recipients; post-transplant infection

Correspondence and offprint requests to: Dr M. R. Narayanan Nampoory, Department of Medicine, Faculty of Medicine, P.O. Box 24923, Safat, 13110 Kuwait.

Introduction

Nocardiosis has emerged as an important opportunistic infection in organ transplant recipients [1]. Recently, Beaman and Beaman comprehensively reviewed published literature and found 140 (21.8%) cases of nocardiosis in organ transplant recipients, of which 81 (58%) were in renal transplant recipients [2]. It manifests as pneumonia (80% of the cases), multiple central nervous system abscesses (10–20%) and/or skin and soft tissue infections (10%) [3]. Even though *N. asteroides* is the commonest, additional *Nocardia* species, namely *N. farcinica* [4] *N. nova* [5] and *N. transvalensis* [6] have also been recognized as emerging human pathogens [7–9].

There are no published reports of human nocardiosis from the Middle-East countries. We present six cases of nocardiosis in renal transplant recipients and discuss our salient clinical, diagnostic, and therapeutic observations.

Subjects

Identification of patients

A retrospective review of case charts of 513 renal transplant recipients from January 1989 to January 1995 at the Mubarak Al-Kabeer University Hospital, Kuwait was done. The cases were identified by the discharge diagnosis of nocardial infection. Information was collected on age, sex, immunosuppressive therapy, preinfection rejection episodes, type of donor, clinical presentation, site of disease, source of the diagnostic material, co-morbid illnesses, species of *Nocardia* isolated, antimicrobial therapy, outcome, duration of follow up and recurrence. All cases had chest X-rays, while CT scan of brain was done when there was central nervous system symptoms and findings.

Immunosuppressive therapy and prophylaxis

Most renal transplant recipients were on triple-drug immunosuppression with prednisolone (1 mg/kg tapered to 10 mg/d in 6 months), cyclosporin A (7 mg/kg per day tapered to 1–2 mg/kg per day in 6 months) and azathioprine (1–1.5 mg/kg per day tapered to 1 mg/kg per day in 6

months). Monoclonal anti-T-cell antibody (OKT3) and anti-lymphocyte globulin (ALG) were not used in the induction protocol. Intravenous methylprednisolone pulses and/or OKT3 were used in the treatment of rejection episodes. All patients had prophylactic oral mycostatin (100 000 units), trimethoprim (160 mg)–sulphamethoxazole (800 mg) (TMP-SMX) and acyclovir (600 mg) regularly for the first 6 months after transplant.

Laboratory evaluation

Histopathological and microbiological evaluation of all specimens was done. Microscopic examination of specimens included wet mount, KOH preparation, Gram's stain, Ziehl–Neelsen stain and modified Kinyoun's stain. The specimens were routinely cultured onto blood, chocolate, MacConkey, Columbia nalidixic acid and charcoal–yeast extract agar and all cultures were incubated in 5% CO₂ (except those on MacConkey agar, which were incubated in ambient air) at 35°C for 48 h. Clinical specimens for fungal isolation were routinely cultured on Sabouraud agar with and without chloramphenicol (50 mg/l) and incubated at room temperature up to 6 weeks.

Nocardia isolates were identified by their characteristic aerobic growth appearing as smooth, orange to cream-coloured colonies with powdery, chalky white, aerial hyphae. Gram and modified Kinyoun's stains were done to confirm their microscopic and partial acid-fast characteristics. Species identification of *Nocardia* isolates was accomplished by physiologic tests, lysozyme resistance and antimicrobial susceptibility patterns [6,10–12]. For antimicrobial susceptibility test, modified Kirby Bauer disc diffusion method was used [13,14].

Results

Analysis of 513 renal transplant recipient files revealed six instances of nocardial infection in four males and two females, giving a disease incidence of 1.2%. Demographic, clinical, laboratory, treatment and outcome details on these six patients are summarized in Tables 1 and 2. The mean age of the patients who had nocardial infection was 46.3 ± 5.2 years (39–60 years). The sources of the donor kidney was cadaver in one, live related in one and live unrelated in four. They had received the renal transplant 3–54 months (mean 16.3 ± 17.7) before the diagnosis of infection.

All patients had fever at the time of initial presentation. Deep-seated abscesses (ischio-rectal, thigh muscle and perinephric), were present in one patient each. The other three patients presented with respiratory symptoms of cough with minimal expectoration. Radiologically lesions were right apical abscess in one, right apical hazy nodular shadows in one and bilateral mid and upper zone infiltrates in one (Figure 1). Two of the patients with respiratory presentation also complained of headache and altered sensorium. CT scan of the brain revealed a single cerebral abscess in one (Figure 2) and multiple abscesses in the other. The latter patient had also signs suggestive of meningeal irritation and evidence of meningitis on spinal fluid examination. The third patient, who had no CNS-related symptoms, had normal brain CT findings.

Nocardia was isolated on culture of the pus obtained from the cutaneous abscesses in three patients, trans-bronchial lavage and fine-needle aspirate specimen in two patients and CSF in the single patient with menin-

Table 1. Salient clinical and laboratory features of renal transplant patients¹ with *Nocardia* infection

Case No./Initials	Age/sex	Donor	Months after transplantation	Days after rejection	Serum creatinine ($\mu\text{mol/l}$)	Presenting manifestations	Associated disease
1/NM	40/F	Cadaveric	54	No rejection	60	Fever, flank pain, abdominal wall-swelling,	Hepatitis, (non-viral) diabetes mellitus
2/DH	53/M	LURD	18	No rejection	92	Fever, cough,	History of pulmn. tuberculosis treatment
3/HA	39/F	LRD	13	No rejection	68	Ischio-rectal abscess	Diabetes mellitus, hepatitis C, hypertension, Candida infection of the groin and oesophagus
4/MK	46/M	LURD	6	No rejection	96	Fever, headache, cough, drowsiness, meningitis	None
5/SA	50/M	LURD	3	3 days after the fifth rejection	132	Fever, cough, chest pain, headache, drowsiness	Neutropenia
6/MA	60/M	LURD	4	No rejection	118	Fever, swelling in the thigh	Non-insulin-dependent diabetes

LURD, live unrelated donor; LRD, live related donor.

¹All the patients were on triple immunosuppression comprising prednisolone, azathioprine, and cyclosporin A.

Table 2. Roentgenographic features, diagnosis and outcome of renal transplant recipients with nocardial infection

Case No.	Site of disease	Radiological findings	Diagnostic material	Nocardia species	Treatment duration	Outcome
1	Perinephric abscess	Chest, normal, CT brain, normal	Pus, abscess wall biopsy	<i>N. asteroides</i>	Cefuroxime TMP/SMX 6 mths	Cured
2	Lung	Fibrotic lung disease with right apical cavitation, CT brain, normal	Fine-needle aspirate lung (+), BAL (-)	<i>N. otitidis-caviarum</i>	TMP/SMX 6 mths	Cured
3	Ischiorectal abscess	Chest, normal	Pus, abscess wall biopsy	<i>N. asteroides</i>	Cefuroxime, TMP/SMX stopped due to liver pathology	Abscess improved; died from candidaemia
4	Multiple cerebral abscesses, lung lesion, meningitis	Chest, hazy shadows in the right apex; CT brain, multiple abscesses	Cerebro spinal fluid (+), BAL-ND	<i>N. farcinica</i>	Piperacillin, Amikacin, Dexamethasone	Died from cerebral nocardiosis
5	Cerebral abscess, lung lesion	Chest, bilateral hazy lesions in both midzones, CT brain, solitary abscess	Bronchial aspirate (+)	<i>N. asteroides</i>	Cefuroxime TMP/SMX 6 mths	Cured
6	Thigh abscess	Chest, normal	Pus	<i>N. asteroides</i>	TMP/SMX 6 mths	Cured

TMP, trimethoprim; SMX, sulphamethoxazole; ND, not done; BAL, bronchoalveolar lavage.

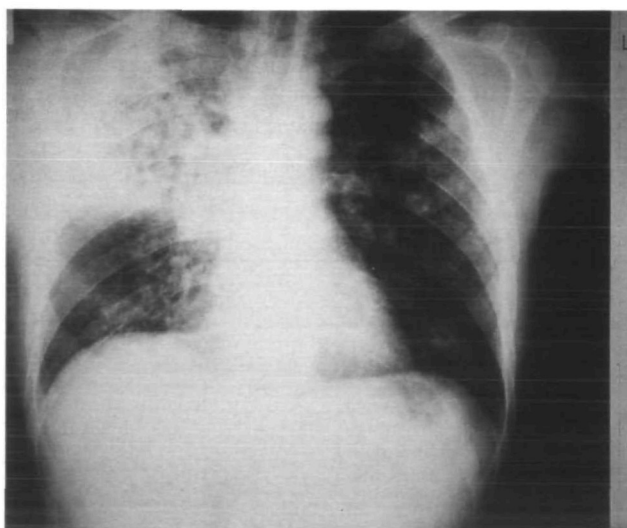


Fig. 1. Chest roentgenogram showing hazy, nodular and infiltrative shadows with areas of breakdown mainly in right apical and left mid-zones.

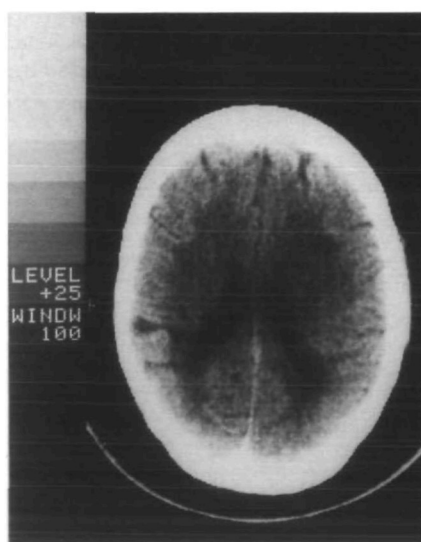


Fig. 2. Computerized tomogram of brain showing single abscess (arrow) in the right parietal region of the cerebrum.

geal symptoms. *Nocardia asteroides* was the offending species in four patients, all three with skin abscesses and one with cerebral abscess and respiratory symptoms. In one patient with cerebral abscess and respiratory symptoms the offending species was *N. farcinica* and in another patient with respiratory involvement alone, the agent was *N. otitidiscaviarum*. The *in vitro* antibiotic sensitivity pattern of the cultured organisms is shown in Table 3. The single isolate of *N. otitidiscaviarum* was resistant to all antibiotics tested

except for amikacin. All four isolates of *N. asteroides* were sensitive to amikacin, cefuroxime, cefotaxime, and ceftriaxone. Three isolates of *Nocardia* were resistant to sulphamethaxazole (SMX) alone or TMP-SMX combination. *In vivo* response to treatment differed, however, to the *in vitro* sensitivity testing. Five patients successfully responded to treatment; two of whom had received only TMP-SMX, and the other three TMP-SMX with cefuroxime. The sixth patient with *N. farcinica* infection succumbed to the disease did not

Table 3. Antimicrobial susceptibility of *Nocardia* isolates

Antibiotic tested	<i>Nocardia</i> isolates ¹ from case					
	1	2	3	4	5	6
Ampicillin	R	R	R	R	S	R
Erythromycin	I	R	R	R	R	R
Carbenicillin	R	R	R	R	R	R
Imipenem	S	R	R	S	S	S
Cefuroxime	S	R	S	S	S	S
Cefotaxime	S	R	S	S	S	S
Ceftriaxone	S	R	S	S	S	S
Cefamandole	I	R	S	R	S	I
Tobramycin	S	R	S	R	S	S
Amikacin	S	S	S	R	S	S
Sulfamethoxazole (SMX)	R	R	S	S	S	R
Trimethoprim (TMP)-SMX	R	R	S	S	S	R

R, resistant, intermediate; S, susceptible.

¹Isolates from case 1, 3, 5 and 6 identified as *N. asteroides*, from case 2 as *N. otitidiscaviarum*, and case 4 as *N. farcinica*.

receive either of the two drugs, but amikacin and piperacillin. The four patients who successfully responded to treatment and were followed up for a mean period of 34 months (15 to 68 months) had no recurrence of the disease.

All six patients who developed nocardial infection were on triple-drug immunosuppression. The infection occurred in the first 6 months in three patients and as late as 54 months in one (Table 1). Episodes of acute graft rejection or its treatment did not relate to the incidence of nocardial infection in all patients except perhaps one (Table 1). Co-morbid conditions that could have contributed to nocardiosis were diabetes mellitus in three, hepatitis in two and neutropenia in one. All patients were HIV negative.

Discussion

The reported incidence of nocardiosis in renal transplant recipients varies from 2 to 20% [15–17]. However, a threefold decrease in the incidence of nocardiosis in post-renal transplant recipients who were on cyclosporin A immunosuppression compared to a historical control group receiving azathioprine–prednisolone was reported by Arduino *et al.* [18]. In our hands, the overall incidence for nocardiosis was 1.2% and all six patients were receiving triple-drug immunosuppression, including cyclosporin A. A significant proportion of our patients (48.4%) had received live unrelated grafts necessitating heavier immunosuppressive drug therapy. Five of the six patients developed nocardiosis while having normal renal function, and hence graft rejection episodes could not be implicated [19,20]. A prolonged steady state of immunosuppression by itself appeared to be the major risk factor in our patients [18]. Three of our patients developed nocardiosis while on TMP-SMX chemoprophylaxis intended for urinary tract and *Pneumocystis*

carinii infection. This would indicate failure of low-dose TMP/SMX chemoprophylaxis against nocardiosis.

There is no clinical syndrome that is pathognomonic of nocardiosis. An acute febrile illness, deep seated abscesses, symptoms and signs of chronic pneumonitis, especially in the upper zones of the chest, and associated meningeal symptoms in an immunosuppressed patient should raise a high index of suspicion for nocardiosis. Those with pulmonary nocardial infection appear to be at a greater risk for systemic spread and consequent cerebral disease than those with localized lesions such as an abscess [21]. An incidence of 16% CNS involvement with nocardiosis has been reported in renal transplant recipients [22]. The most common clinical CNS manifestation is single or multiple abscesses affecting any part of the brain [2]. Isolated meningitis can also occur [23]. Fever, headache and depressed sensorium were the cardinal features in our two patients with cerebral nocardiosis. Skin is reportedly a common site of dissemination of infection in nocardiosis and Wilson *et al.* [22] noted a 13% incidence of skin involvement in 88 renal transplant recipients. *Nocardia asteroides* is the most frequently isolated species from these infections [3]. In our three patients with deep-seated abscesses, skin was the most probable route of entry of infection as they had no other demonstrable site of involvement to indicate an alternate route. Spread of infection into the perinephric region from a cutaneous source, as observed in one of our patients, has not been reported previously. *Nocardia otitidiscaviarum* is more often reported to cause localized cutaneous disease [21] while our only patient had respiratory involvement and no cutaneous manifestations.

Our studies on *in vitro* sensitivity of *Nocardia* favour the use of cefuroxime and amikacin most and that of sulphamethoxazole (singly) the least. However, the *in vivo* response to antibiotics in our patients differed in that two of our patients who were on TMP-SMX alone responded satisfactorily. Such disparity between clinical response and *in vitro* sensitivity testing has been previously reported [24,25]. Cefuroxime, because of its excellent CNS penetration and anti-nocardial activity appears to be an appropriate drug of choice in nocardial CNS involvement. We have used cefuroxime in combination with TMP-SMX rather than by itself with excellent clinical response. The one patient with *N. farcinica* infection who had multiple brain abscesses and respiratory involvement, alternate antibiotic therapy proved unsuccessful. This species is known for its propensity to cause more serious systemic infection in both normal and immunocompromised hosts, and to show a marked degree of resistance to multiple microbial agents [26]. Combined use of TMP-SMX and cyclosporin A is reported to cause adverse synergistic nephrotoxic interaction [27,28]. We have used this drug combination in five of our patients with normal renal function, there were no adverse effects and no dose modification was required.

Definitive diagnosis by demonstration of the organ-

ism was reached by an aggressive approach such as bronchoscopic lavage, fine-needle aspiration of the affected region, CSF examination, or aspiration of pus from the abscess. Routine examination of the sputum, urine, or blood for nocardiae were unhelpful. *Nocardia* grows slowly in culture, causing delay in diagnosis. Rapid diagnostic tests based on serological techniques or DNA amplification are obviously needed.

In conclusion, we advocate a high index of suspicion for nocardiosis in susceptible hosts presenting with deep tissue abscesses, infiltrative pulmonary lesions, or cerebral abscesses, and an active approach in obtaining optimal specimens for diagnostic studies and early institution of appropriate antibiotic therapy. TMP-SMX in combination with cefuroxime seems to be a highly effective therapy in nocardiosis.

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