Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

Nocardiosis following solid organ transplantation: a single-centre experience

Silve Wiesmayr,[1] Ingrid Stelzmüller,[1] Walther Tabarelli,[1] Derinique Bargehr,[1] Ivo Graziadei,[2] Michael Freund,[3] Ruth Ladurner,[1] Wolfgang Steurer,[1] Christine Geltner,[4] Walter Mark,[1] Raimond Margreiter[1] and Hugo Bonatti[1]

1 Department of General and Transplant Surgery, University Hospital of Innsbruck, Innsbruck, Austria
2 Department for Gastroenterology and Hepatology, University Hospital of Innsbruck, Innsbruck, Austria
3 Department for Radiology, University Hospital of Innsbruck, Innsbruck, Austria
4 Department for Pulmonology, Krankenhaus Natters, in der Stille, Natters, Austria

Keywords
infection, nacardiosis, transplantation.

Correspondence
Hugo Bonatti MD, PhD, Department of General and Transplant Surgery, University Hospital of Innsbruck, Anichstraße 35, 6020 Innsbruck, Austria. Tel.: ++43 512 504 22604; fax: ++43 512 504 22605; e-mail: hugo.bonatti@uklibk.ac.at

Received: 8 February 2005
Revision requested: 3 March 2005
Accepted: 3 May 2005

doi:10.1111/j.1432-2277.2005.00177.x

Summary

Nocardiosis is a localized or disseminated bacterial infection caused by aerobic Actinomyces that commonly affects immunocompromised hosts. The aim of this study was to retrospectively review clinical course and outcome of nocardiosis in solid organ recipients at our centre. Five cases of nocardiosis were identified in a series of more than 4000 consecutive solid organ transplants performed at Innsbruck university hospital during a 25-year period. Of the five patients with nocardiosis, two had undergone multivisceral, one liver, one kidney and one lung transplantation. Three patients with *Nocardia asteroides* infection were treated successfully and recovered from their infectious disease, however, one lost his renal graft following withdrawal of immunosuppression. The lung recipient recovered from nocardiosis but died later on from *Pseudomonas* pneumonia. One multivisceral recipient died from *Nocardia farcinica*-disseminated infection. Nocardiosis is a rare, difficult-to-diagnose-and-treat complication following solid organ transplantation. Intestinal recipients might be at increased risk to develop this infection.

Introduction

Solid organ transplantation has emerged as the treatment of choice for end-stage organ failures, with the burden of life-long immunosuppression for the organ recipient. Thus, infection dominates the peri-operative as well as the post-operative period, with considerable potential of life-threatening bacterial sepsis and death reported in most transplant series. Nocardia – a rare but dangerous micro-organism that is associated with excessive mortality rates – has been reported as a causative agent of infections in the immunocompromised host and infants. Solid organ recipients, stem cell recipients, patients with malignancies, the HIV population and other patient populations with immunodeficiency are at highest risk for this disease [1]. Nocardia infections have been reported in heart, liver, lung and kidney transplant recipients [2–5]; however, presentation in multivisceral recipients has not been reported yet. Usually nocardiosis presents with fever, cough, chest pain and dyspnoea.

In our series we aimed to retrospectively review the clinical course and outcome of all cases of Nocardiosis in solid organ transplantation at our transplant centre.

Patients and methods

Between 1 January 1977 and 31 December 2004 more than 4000 solid organ transplants were performed at the Innsbruck University hospital. There were 2527 renal, 746 liver, 368 pancreas, 241 cardiac, 122 lung, 24 intestinal, 24 islet and two hand transplants. Within the entire cohort a total of five patients became symptomatic with nocardiosis including two multivisceral, one liver, one renal and one lung recipient.

Surgical technique and perioperative management were performed according to standard techniques. Standard immunosuppression consisted of Calcineurin inhibitor-based triple drug therapy using ATG or IL2 receptor antagonist induction in a variety of cases. The two multivisceral recipients received tacrolimus (trough levels 15–20 ng/ml), steroids (20 mg) and azathioprine (100 mg) for immunosuppression, the lung recipient recipients cyclosporin A (CsA), azathioprine and steroids with ATG induction, the liver recipient CsA, azathioprine and steroids, the adult renal recipient TAC, mycophenolate mofetil (MMF) and steroids.

Nocardia was identified from bronchoalveolar lavage (BAL) in one case, pleural effusion in another case, percutaneous lung biopsy in two cases and a removed inguinal lymph node/liver abscess in the last case.

Results

Nocardia asteroides was most commonly isolated. Only for intestinal recipients (2 of 20 patients in our series) there seems to be an increased risk for nocardiosis. Four of the five patients also experienced other infectious complications, including pneumonia, sepsis, UTI, invasive Aspergillosis, *Candida* oesophagitis. Three developed cytomegalovirus (CMV) infection or disease prior to the outbreak of nocardiosis. Three patients with *N. asteroides* infection were treated successfully and recovered from their infectious disease, however, one lost his renal graft following withdrawal of immunosuppression. The lung recipient recovered from nocardiosis but died later on from Pseudomonas pneumonia. One multivisceral recipient died from multiorgan failure due to disseminated *N. farcinica* and pulmonary *Pseudomonas aeruginosa* and *Aspergillus fumigatus* superinfection. Table 1 shows demographic and Table 2 clinical data of the five patients.

Case 1

The first case affected a 51-year-old male bilateral lung recipient. Antimicrobial prophylaxis included Cefamandol (2 g q 8 h) and Fosfomycin (4 g q 8 h). The early

Table 1. Demographic data.

	Gender	Age	Date of transplant	Graft	Underlying disease	Initial immunosuppression	Perioperative prophylaxis	CMV match (donor/recipient)	Risk factors
1	Male	51	1 April 1996	Lung	Epitheloid hemangioendothelioma	CsA, AZA, steroids	Cefemandol/ Fosfomycin	Negative/ negative	Long-term ventilation
2	Male	63	27 November 1997	Intestine	Carcinoid	TAG, AZA, steroids	Piperacillin/ Tazobactam	Positive/positive	Poor medical condition
3	Male	57	1 October 1999	Liver	HCV	CsA, AZA, steroids	Piperacillin/ Tazobactam	Positive/positive	Rejection
4	Female	38	3 July 2000	Intestine	Gardner syndrome	TAG, AZA, steroids	Piperacillin/ Tazobactam	Positive/positive	retransplant, rejection
5	Male	64	15 August 2004	Kidney	Diabetic nephropathy	TAG, MMF, steroids	Ceftriaxon	Negative/ negative	Advanced age, coronary artery disease, rejection

Tx, transplant; HCV, hepatitis C virus; CsA, cyclosporin A; TAG, tacrolimus; AZA, azathioprine; MMF, mycophenolate mofetil.

Table 2. Clinical data.

	Onset of nocardiosis post-Tx (weeks)	Isolation of *Nocardia*	*Nocardia* species	Other infections	CMV infection disease	Antimicrobial treatment	Cure	Cause of death	Survival post-Tx (months)
1	1	Pleural effusion	No subtyping	Bacterial pneumonia, chronic diarrhoea	Yes	IMPS	Yes	Pneumonia	3
2	12	Lung biopsy	*N. asteroides*	Sepsis, HSV infection, *Candida* oesophagitis	No	TMPS + Doxicycline	Yes	Tumour progression	21
3	5	Lung biopsy	*N. asteroides*	No	No	IMPS	Yes	Alive	65
4	4	Liver abscess	*N. farcinica*	Urinary tract infection, MRSA sepsis	Yes	TMPS; Ciprofloxacin Amoxicillin/Clavulanic acid, Imipenem/ Cilastatin	No	Nocardiosis	1
5	8	Bronchoalveolar lavage	*N. asteroides*	Aspergillosis	Yes	TMPS, Linezolid	Yes	Alive, renal graft loss	7

Tx, transplant; CMV, cytomegalovirus; EBV, Epstein–Barr virus; IMPS, trimthoprim–sulfamethoxazole.

post-transplant course was complicated by pulmonary arterial stenosis which required surgical revision, diarrhoea and bilateral pneumonia which required reintubation on the fifth postoperative day. From BAL *Enterococcus faecium* was isolated and Vancomycin (1 g q 12 h) in combination with Imipenem/Cilastatin (1 g q 8 h) was started. Nocardia was isolated from pleural effusion and treatment changed to trimethoprim/sulfamethoxazol (TMPS). The patient required tracheostomy and long-term ventilator support. *Candida albicans* pneumonia was treated with liposomal amphotericin B (3 mg/kg/day) and *P. aeruginosa* pulmonary infection with ceftazidime (1 g q 6 h). Ganciclovir was given for CMV infection. The patient was transferred on day 35 post-transplant to his home hospital in stable condition where he died 1 month later from intractable pulmonary infection.

Case 2

Case 2 relates to a 63-year-old man who underwent multivisceral transplantation. He developed multiple infectious episodes including deep wound infection and an intestinal fistula requiring surgical revision, enterococcal and *Corynebacterium jeikeum* sepsis, MRSA port-a-cath infection, *Candida* oesophagitis, herpes stomatitis and genital herpes. He was discharged 6 weeks post-transplant with a well functioning graft. Three months post-transplant the patient was readmitted with fever as high as 39.5 °C and an elevated CRP of 24.5 mg/dl. Blood cultures grew MRSA and enterococci. Despite treatment with Vancomycin (1 g q 12 h) the patient did not improve. CT scan revealed a small pulmonary infiltrate within the left lung and CT-guided percutaneous biopsy was carried out (Fig. 1). Histological examination revealed a granulomatous lesion and *N. asteroides* resistant to Imipenem–Cilastatin was grown. Oral TMPS (800 mg/160 mg once daily) and Doxycycline (200 mg q 12 h) were administered. Tacrolimus was withdrawn and immunosuppression tapered and changed to prednisone (10 mg once daily) and mycophenolic acid (2 g q 12 h). The patient fully recovered from Nocardiosis and was discharged after 4 weeks of antibiotic therapy with a well functioning graft. Subsequently he developed HCV-recurrence and several bacteraemic episodes. The patient died from tumour progression 2 years post-transplant.

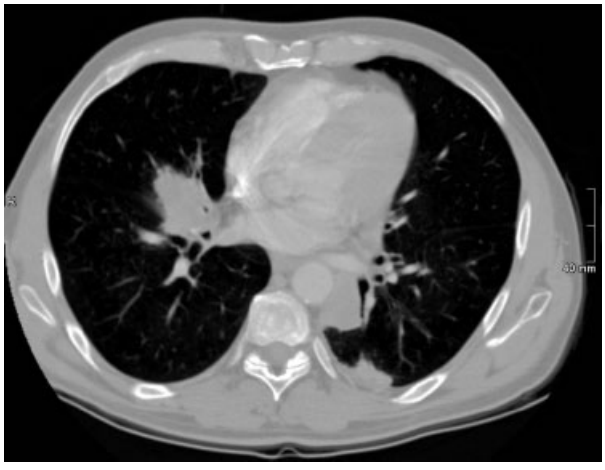

Figure 1 CT scan: Nocardiosis of the lung.

Case 3

Case 3 relates to a 57-year-old male liver recipient. Acute rejection on the 10th postoperative day was successfully treated by bolused steroids. He was discharged in stable condition with good graft function on day 24 post-transplant. On day 32 the patient presented with fever as high as 40 °C, non-productive cough and dyspnoea. Laboratory evaluation showed leucocytosis, elevated CRP and Neopterin levels and elevated liver function parameters. Empiric antimicrobial treatment consisted of Ceftazidime (2 g q 8 h) with no clinical improvement. CT scan showed multiple pulmonary infiltrations. From percutaneous biopsies *N. asteroides* were grown. Nocardiosis was successfully treated with TMPS (800 mg/160 mg once daily) and tapering of immunosuppression. The patient is still alive with a well functioning liver allograft more than 3 years following his transplant.

Case 4

The fourth case affected a 38-year-old woman who underwent multivisceral transplantation. Postoperative course was complicated by multiple episodes of acute graft rejection and several bacterial and fungal infections. Despite oral ganciclovir prophylaxis the patient developed CMV infection. Due to progressive dysfunction of the intestinal part of the graft the patient was retransplanted. Two weeks following retransplantation another rejection episode was treated with bolused steroids. During the fourth week post retransplant the patient developed inguinal lymphadenopathy as well as abscesses in liver segments 2 and 3 (Fig. 2). The abscess was percutaneously drained and *N. farcinica* was cultured. Therapy with TMPS (800 mg/160 mg once daily) was initiated. As the patient developed severe thrombopenia, treatment was switched to Ciprofloxacin (200 mg q 12 h) in combination with Amoxicillin/Clavulanic acid (2.2 g q 8 h). Intrahepatic abscesses did not improve and finally it was decided to perform explorative laparotomy. Multiple liver abscesses were drained and again *N. farcinica* was isolated. CT scan demonstrated diffuse bilobar pulmonary

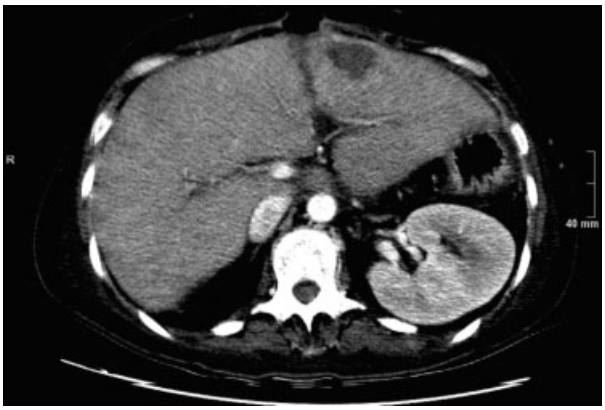

Figure 2 CT scan: Nocardiosis of the liver.

infiltrates and from BAL again *Nocardia farcinica* was cultured. Additional *P. aeruginosa* was isolated from the abscesses and treated with Ceftazidim. Due to progression of nocardiosis Imipenem/Cilastatin was started and simultaneously tacrolimus was tapered to trough levels of 4–6 ng/ml. The patient became progressively worse, liver abscesses did not improve and following another septic episode the patient died from multi-organ failure.

Case 5

The last patient was a 65-year-old renal recipient. Acute rejection was successfully treated with bolused steroids. He was discharged from our hospital but readmitted to a peripheral hospital for CMV disease. GCV caused leucopenia and subsequently the patient developed pulmonary infiltrates. From BAL *N. asteroides* was cultured and treated with TMPS. The patient slowly recovered, however, renal function further deteriorated following withdrawal of immunosuppression. The graft finally was removed due to rejection. The patient developed bronchial aspergillosis which was successfully treated with Voriconazole. Pulmonary infiltrates gradually improved and the patient was discharged in satisfactory condition after 3 months hospitalization.

Discussion

This series analyses our experience with nocardiosis in solid organ recipients. All patients in this series presented with Nocardiosis within the first 12 weeks after transplantation. Whereas *N. asteroides* seems to be well treatable with TMPS, no agent with satisfactory activity was found to treat *N. farcinica*. Intestinal recipients might be at increased risk to develop this infection.

In general, nocardiosis is a rare infectious disease, with a reported prevalence of 0.7–4%, with a significantly higher incidence amongst transplant recipients [6–8]. Still it should be considered as a causative agent in the differential diagnosis of pulmonary diseases in the immunocompromised host. According to the literature the most frequent predisposition for Nocardial infection is organ transplantation [9]. Nocardiosis is often associated and complicated by fungal superinfections manifesting with analogous clinical features [10–12]. Nocardia is a slow growing, variably acid-fast, Gram-positive, filamentous, aerobic actinomycete found in the soil and decaying organic matter [1,9,13]. Apart from the most common species *N. asteroides* (types 1 and 4), other species including *N. farcinica*, *N. transvalensis*, *N. brasiliensis*, *N. pseudobrasiliensis*, *N. brevicatena*, *N. nova* and *N. otiti discaviarum* are described subforms [14].

The micro-organism uses the respiratory tract as primary entry and has a devastating potential to invade pulmonary blood vessels and subsequently metastasize to skin, central nerve system, thyroid gland, kidney or eyes [15–17]. In immunocompetent patients *Nocardia* manifests with cutaneous, subcutaneous and lymphocutaneous lesions, whereas in immunocompromised individuals it is associated with pneumonia in up to 88%; at least six basic forms of clinical manifestation may be noted: pulmonary nocardiosis, systemic nocardiosis (involving at least two body sites), CNS nocardiosis, extrapulmonary nocardiosis, cutaneous, subcutaneous and lymphocutaneous nocardiosis and actinomycetoma [9]. Approximately two-thirds of cases present as localized diseases and one-third as disseminated Nocardiosis [3]. Nocardia can be the leading cause of central nervous system abscesses, with a prevalence as high as 10–20% [2]. The clinical features of our case series are similar to those described in other series; however, we have not observed brain abscesses or skin lesions in our patients. CMV might play a role in the development of Nocardiosis through its immunomodulating effect [18]. In this series three patients developed CMV infection/disease prior to the outbreak of Nocardiosis. Additionally four of the five patients presented with severe bacterial and fungal infections (pneumonia, sepsis, UTI, invasive Aspergillosis, *Candida* oesophagitis).

Isolation of *Nocardia* in pure culture remains the gold standard for detection, though it can take several days until colony-forming units can be seen, and, if culture is mixed, diagnosis might be delayed even further [13,19]. Methods for confirmation and specification include hydrolysis characteristics, biochemistry and antimicrobial susceptibility tests. These assays can take up to 8 weeks and are not performed routinely at all microbiology laboratories. Innovative molecular detecting techniques, such as RFLP for specification can last 1–2 days, but do still require culturable organisms.

In general, *Nocardia* is susceptible to TMPS which functions as the first-line therapy. Although *in vitro* sensitivity tests might have assessed resistance to sulfa drugs, there exists in fact a great deal of discrepancy between *in vitro* testing and the clinical response [3,9]. Development of antibiotic resistance is indeed a concern. The prophylactic application of TMPS for PCP prophylaxis should also cover *Nocardia* spp. However, systemic nocardiosis has been reported even in patients receiving TMPS prophylaxis [20]. In our series sulfa resistance was not observed. Only in the female with Gardner syndrome TMPS had to be withdrawn due to development of a thrombocytopenia, a side effect not mentioned in other case reports so far. TMPS is still considered the first-line therapy; however, it exerts only a bacteriostatic effect and is associated with numerous severe side effects. Thus, combined treatment with carbapenems and amikacin or quinolones with bactericidal activity and less toxicity might offer alternative options, with agents such as minocycline, quinolones or linezolid used for sequential long-term oral treatment [21–23]. Additionally, surgery and reduction or even temporary withdrawal of immunosuppressive agents might be of relevance to cure Nocardiosis.

Two of our five patients were multivisceral transplant recipients and the *N. farcinica* case represents the first reported case in this setting. One case of *N. asteroides* prostatitis in a small bowel recipient was reported with good outcome [6]. The high level of immunosuppression required in intestinal recipients is assumed to be the most important risk factor. Coinfection and superinfection with other pathogens and recurrent CMV infection might be additional indicators of over-immunosuppression [24]. Whereas the localized *N. asteroides* infection could be controlled, *N. farcinica*-disseminated disease was lethal. Disseminated nocardiosis, in particular with cerebral abscess, carries the poorest prognosis with a related mortality as high as 90% [4]. Recent improvements in detection and treatment resulted in decreased mortality rates [25].

In conclusion, we recommend a high grade of suspicion and awareness of Nocardiosis in solid organ recipients who require intensified immunosuppression and present with a pulmonary infiltrate. BAL and percutaneous lung biopsy should be performed in order to obtain accurate diagnosis. Microbiology laboratories should attempt to identify *Nocardia* to species level and *in vitro* susceptibility tests should be performed in order to optimize antimicrobial treatment.

References

1. Lederman ER, Crum NF. A case series and focused review of nocardiosis: clinical and microbiologic aspects. *Scand J Urol Nephrol* 2004; **38**: 168.
2. Husain S, McCurry K, Dauber J, Singh N, Kusne S. Nocardia infection in lung transplant recipients. *J Heart Lung Transpl* 2002: **21**: 354.
3. Peraira JR, Segovia J, Fuentes R, *et al.* Pulmonary nocardiosis in heart transplant recipients: treatment and outcome. *Transplant Proc* 2003; **35**: 2006.
4. Shin JH, Lee HK. Nocardial brain abscess in a renal transplant recipient. *Clin Imaging* 2003; **27**: 321.
5. Vandjme A, Pageaux GP, Bismuth M, *et al.* Nocardiosis revealed by thyroid abscess in a liver–kidney transplant recipient. *Transpl Int* 2001 **14**: 202.
6. Qu L, Strollo DC, Bond G, Kusne S. *Nocardia prostatitis* in a small intestine transplant recipient. *Transpl Infect Dis* 2003; **5**: 94.
7. Queipo-Zaragoza JA, Broseta-Rico E, Alapont-Alacreu JM, Santos-Durantez M, Sanchez-Plumed J, Jimenez-Cruz JF. Nocardial infection in immunosuppressed kidney transplant recipients. *Scand J Urol Nephrol* 2004; **38**: 168.
8. Canet S, Garrigue V, Bismuth J, *et al.* Nocardiosis – is it frequently observed after the introduction of new immunosuppressive agents in renal transplantation? *Nephrologie* 2004; **25**: 43.
9. Beaman BL, Beaman L. Nocardia species: host–parasite relationships. *Clin Microbiol* 1994; **7**: 213.
10. Dorman SE, Guide SV, Conville PS, *et al.* Nocardia infection in chronic granulomatosus disease. *Clin Infect Dis* 2002; **35**: 390.
11. McNeil MM, Brown JM, Magruder CH, *et al.* Disseminated *Nocardia transvalensis* infection: an unusual opportunistic pathogen in severely immunocompromised patients. *J Infect Dis* 1992; **165**: 175.
12. Monteforte JS, Wood CA. Pneumonia caused by *Nocardia nova* and *Aspergillus fumigatus* after cardiac transplantation. *Eur J Clin Microbiol Infect Dis* 1993; **12**: 112.
13. Nocardia infections. *Am J Transplant* 2004; **4** (Suppl. 10): 47.
14. Kiska DL, Hicks K, Pettit DJ. Identification of medically relevant *Nocardia* species with an abbreviated battery of tests. *Clin Microbiol* 2002; **40**: 1346.
15. Carriere C, Marchandin H, Andrieu JM, *et al. Nocardia thyroiditis*: unusual location of infection. *J Clin Microbiol* 1999; **37**: 2323.
16. Suppiah R, Abraham G, Sekhar U, *et al. Nocardial endophtalmitis* leading to blindness in a renal transplant recipient. *Nephrol Dial Transplant* 1999; **14**: 1576.
17. Frangie C, Morel D, Sassoust G, *et al.* A rare infection in a renal transplant recipient. *Nephrol Dial Transplant* 2001; **16**: 1285.
18. Paya CV. Indirect effects of CMV in the solid organ transplant patient. *Transpl Infect Dis* 1999; **1** (Suppl. 1): 8.
19. Corti ME, Villafane-Fioti MF. Nocardiosis: a review. *Int J Infect Dis* 2003; **7**: 243.
20. Lopez FA, Johnson F, Novosad DM, Beaman BL, Holodniy M. Successful management of disseminated *Nocardia transvalensis* infection in a heart transplant recipient after

development of sulfonamide resistance: case report and review. *J Heart Lung Transplant* 2003; **22**: 492.
21. Moylett EH, Pacheco SE, Brown-Elliott BA, *et al.* Clinical experience with linezolid for the treatment of nocardia infection. *Clin Infect Dis* 2003; **36**: 313.
22. Kanemitsu K, Kunishima H, Saga T, *et al.* Efficacy of amikacin combinations for nocardiosis. *Tohoku J Exp Med* 2003; **201**: 157.
23. Gombert ME, Berkowitz LB, Aulicino TM, duBouchet L. Therapy of pulmonary nocardiosis in immunocompromised mice. *Antimicrob Agents Chemother* 1990; **34**: 1766.
24. Rubin RH. Prevention and treatment of cytomegalovirus disease in heart transplant patients. *J Heart Lung Transplant* 2000; **19**: 731.
25. Wilson JP, Turner HR, Kirchner KA, Chapman SW. Nocardial infections in renal transplant recipients. *Medicine (Baltimore)* 1989; **68**: 38.