Original Article

Nocardiosis in Renal Allograft Recipients

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Abstract

Introduction: The aim of the study was to study the clinical profile and outcomes of nocardiosis in renal allograft recipients. **Methods:** This was a retrospective study of clinical outcomes in consecutive renal allograft recipients with *Nocardia* infection over a 22-year period (2000–2022) from a tertiary care center in Southern India. The clinical data were obtained from electronic medical records and patient files. **Results:** A total of 1970 patients underwent renal transplantation at Christian Medical College, Vellore, India, between January 1, 2000, and December 31, 2022. During this period, 26 patients were diagnosed to have *Nocardia* infection. Half (50%) of the patients had fever and cough as their initial presentation, 7 (26.9%) patients presented with cutaneous abscesses, 2 (7.6%) patients were incidentally detected to have lung nodules during routine follow-up, 2 (7.6%) patients presented with headache accompanied by fever, and 3.8% had graft abscess. The diagnosis was made by isolating the organism in culture from one or more of the following samples: sputum, blood, pus, or lung biopsy (either computed tomography [CT]-guided or bronchoscopic aspirate culture). Eight patients required bronchoscopy and two patients required CT-guided biopsy for obtaining samples for diagnosis. All patients were similarly managed initially with a reduction of immunosuppression and appropriate antibiotics as per culture sensitivity. All 26 patients responded to induction treatment with meropenem (or imipenem) and trimethoprim–sulfamethoxazole (co-trimoxazole) followed by maintenance treatment with co-trimoxazole. Five (19.2%) out of 26 patients received Minocycline in induction and maintenance treatment regimens as in four patients isolates were resistant and one patient had allergic reaction to Cotrimoxazole. All patients had stable graft function. Two patients succumbed after 2 months of diagnosis with Gram-negative sepsis. **Conclusions:** At present, there exists no single serological test to diagnose *Nocardia* infection in patients. Multiple initially obtained cultures may be negative because of the slow growth of the organism and variable colony morphology. Hence, infected specimens should be obtained by aggressive approaches if the index of suspicion is high. Procedures such as bronchoscopic lavage and aspiration of abscess are invaluable toward making a diagnosis. In our study, eight patients required invasive diagnostic procedures such as bronchoalveolar lavage and CT-guided lung biopsy since initial Gram stain and sputum culture were negative. In conclusion, it is crucial to maintain a high level of suspicion and conduct thorough investigations among post renal transplant recipients. This approach facilitates early diagnosis, prompt initiation of appropriate treatment which helps prevent the spread of disease.

Keywords: Bronchoalveolar lavage, carbapenems, computed tomography, co-trimoxazole, cutaneous nocardiosis, disseminated nocardiosis, minocycline, pulmonary nocardiosis, transbronchial lung biopsy

Introduction

Opportunistic infections remain an important cause of morbidity and mortality in renal allograft recipients. Nocardiosis is a rare, life-threatening opportunistic infection caused by Gram-positive filamentous bacteria in the environment that predominantly affects immunocompromised patients.[1] Inhalation is the most common route of entry of *Nocardia*, but the infection can spread through ingestion and direct inoculation of the skin.[2] Renal allograft recipients have the lowest *Nocardia* infection rate compared to other solid-organ allograft recipients.[3,4] The incidence of nocardiosis among renal allograft recipients has been reported to be between 0.7% and 2.6%.[5-7] Nocardiosis most commonly involves the lungs but can disseminate to other organs through contiguous or hematogenous spread. Disseminated nocardiosis, defined as *Nocardia* infection involving two or more organ systems, mandates early detection and initiation of treatment because

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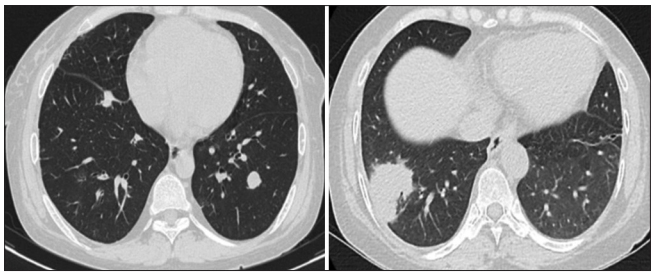

Figure 1: (Left side) multiple nodular parenchymal lesions in both lungs. (Right side) peripheral consolidatory mass lesion noted involving the lateral basal segment of the right lower lobe

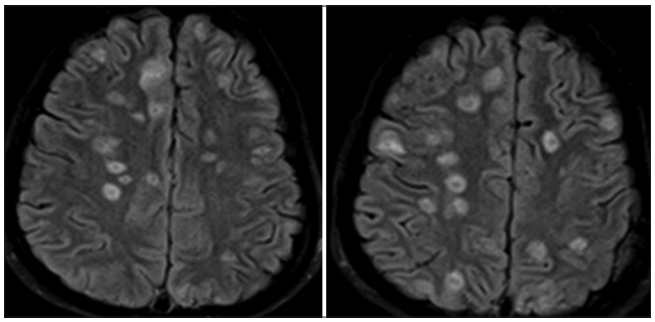

Figure 2: Multiple, small, well-defined, ring-enhancing lesions of varying sizes in the both cerebral and cerebellar hemispheres with involvement of deep gray matter and midbrain. Lesions show the rim of T2-weighted hypointensity and central hyperintensity with perilesional edema and diffusion restriction

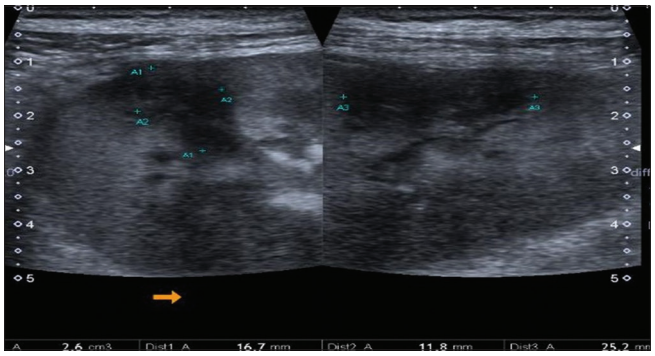

Figure 3: Graft kidney showing 1.6 cm ×1.1 cm ×2.3 cm abscess

of its associated high morbidity and mortality. This study was done to determine the clinical presentation, risk factors, frequency of occurrence, drug susceptibility, and outcome in renal allograft recipients with *Nocardia* infection.

Methods

This was a retrospective analysis of renal allograft recipients from January 2000 to December 2022 at Christian Medical College, Vellore, India, aged 18 years or older, who had *Nocardia* infections. This study was approved by the Institutional Ethics Committee (IRB minute number: 13641, dated December 2, 2020). The cases were identified from the electronic medical records and patient case records maintained in the microbiology department and renal transplant outpatient clinic. A case of nocardiosis was defined as a renal allograft recipient with microbiological confirmation of infection with *Nocardia* species from any site with associated clinical features suggestive of infection. The data collected included demographics, clinical presentation, and time of occurrence since transplantation, diagnosis, treatment, antibiotic therapy and prophylaxis, immunosuppressive regimens, episodes of rejection, and outcome.

Results

A total of 1970 patients underwent renal transplantation during the study period. Twenty-six renal allograft recipients were diagnosed with nocardiosis in this cohort with an incidence of 1.31%. Twenty-three patients (88.4%) received live-related donor kidney transplantation with Basiliximab induction and three patients (11.5%) received deceased donor renal transplantation with Anti Thymocyte Globulin (ATG) as induction agent.

The mean age at diagnosis was 45.4 ± 11.8 years, with a male–female ratio of 5:1. Nocardiosis was localized exclusively in the lung in 16 (61.5%) patients as depicted in Figure 1, 7 (26.9%) had cutaneous abscesses (7.69%), 2 had disseminated nocardiosis involving pulmonary system and central nervous system (CNS) As depicted in Figure 2, and 1 (3.84%) patient had graft abscesses as depicted in Figure 3. The *Nocardia* species identified were *Nocardia asteroides* in 5 patients, *Nocardia beijingensis* in 3 patients, *Nocardia cyriacigeorgica* in 2 patients, *Nocardia wallacei* in 1 patient, *Nocardia farcinica* in 1 patient, and in 14 instances, the exact species could not be identified. All isolates were susceptible to carbapenems and co-trimoxazole except *N. wallacei* and *N. beijingensis* which are resistant to co-trimoxazole. All patients with pulmonary and cutaneous nocardiosis responded to the induction treatment with renal-adjusted doses of imipenem and co-trimoxazole for 6 weeks followed by 6 months of maintenance therapy with co-trimoxazole. Minocycline was used in two patients who had co-trimoxazole-resistant nocardiosis and in one patient who had an allergy to co-trimoxazole. The mean time of developing *Nocardia* infection was 4.6 ± 2.5 years of posttransplantation. Two patients died because of refractory septic shock. Graft function was stable for all patients during infection. The mean tacrolimus trough level (C0) was 8.2 ± 1.6 ng/ml, cyclosporine trough level (C0) was 180.3 ± 102.2 ng/ml, and mycophenolate area under curve was 58.3 ± 3.5 mg.h/L at the time of diagnosis of *Nocardia* infection, all of which are slightly higher levels as per posttransplant duration. A history of rejection within 6 months of nocardiosis was present in 23% (6/26) of patients. Acute cellular rejection (ACR) was present in 4 patients and treated with methylprednisolone pulse. One patient had acute antibody-mediated rejection (ABMR), which was treated with methylprednisolone, plasmapheresis, and rituximab. One patient had combined ACR and ABMR. They were treated with methylprednisolone pulse, plasmapheresis, antithymocyte globulin, and rituximab. The demographic details, transplant details, timing of nocardiosis, methods of diagnosis, and treatment details are summarized in Table 1.

Discussion

Nocardiosis is an uncommon opportunistic infection caused by Gram-positive and weakly acid-fast positive bacteria. Four species have been reported to be pathogenic to humans, with *N. asteroides* accounting for most infections.[8] *Nocardia* infections among renal allograft recipients are infrequent. We found a combined incidence of 1.46%, which is similar to previously reported values. Nocardiosis occurs generally in immunosuppressed patients, including those with impaired cellular immunity, granulocyte function, and humoral immunodeficiency. Common conditions that predispose to disease include transplantation, high-dose corticosteroids, human immunodeficiency virus infection, uncontrolled diabetes mellitus, and alcoholism.[9] The use of high-dose steroids, multiple rejection episodes, and neutropenia has been reported as a risk factor for infections among renal allograft recipients.[10,11] In our study, four patients had ACR, one patient had ABMR, and one patient had combined ACR and ABMR. The patients were treated with antirejection therapy as per the protocol including intravenous methylprednisolone, plasma exchanges, and rituximab. One patient received ATG for resistant ACR before infection, as mentioned in Table 2.

A variety of clinical syndromes may be seen with *Nocardia* infections. Localized pulmonary manifestations are the most frequent, being reported in 60% of cases nearly similar to the frequency identified in our study (53.8%). Disseminated disease results from hematogenous or lymphatic spread. Secondary CNS infection is the most common site of dissemination, accounting for 20%–38% of cases, followed by the skin in 9%–15%.[5] However, we found cutaneous involvement in 26% followed by CNS involvement only in 2 of the 26 cases accounting for 7.6%. Two patients were incidentally detected to have pulmonary nodules during routine follow-up. The most common radiological presentation in pulmonary nocardiosis is lung consolidation seen in 12 (75%) of 16 cases, 2 (7.7%) of the 26 patients had isolated lung nodules, and 4 patients had consolidation and pleural effusion.

Prophylaxis with co-trimoxazole is primarily used to reduce the risk of urinary tract infections and *Pneumocystis jirovecii* pneumonia in renal allograft recipients.[12] In our study, nearly a third of the infections occurred when on co-trimoxazole prophylaxis, indicating that co-trimoxazole did not entirely prevent the development of nocardiosis.

No prospective randomized trials have been done to determine the most effective therapy for nocardiosis.[13] Most authorities recommend co-trimoxazole as part of first-line therapy for nocardiosis.[14,15] Despite the success of co-trimoxazole in the treatment of nocardiosis, combination therapy with other agents is warranted in patients with severe infections.

It is judicious to treat all patients with cutaneous nocardiosis with systemic antibiotics because of the possibility of covert widespread disease. Single-agent oral therapy is usually sufficient for patients with cutaneous disease from an inoculation injury. Empiric monotherapy regimens for patients with normal renal function include co-trimoxazole (5–10 mg/kg of the trimethoprim component orally in two divided doses) and, less preferably, minocycline (100 mg orally twice daily).

Severe nocardiosis includes cases of pulmonary disease with extensive lung involvement or those with direct spread from the lung to pleura, chest wall, or another contiguous organ. Severe infection also includes all cases of disseminated disease (involvement of more than one noncontiguous site) or CNS disease. Initial treatment (i.e., induction therapy) should be administered intravenously for at least 3–6 weeks and/or until clinical improvement is documented. We use at least two intravenous agents during the induction phase of therapy for all patients with severe disease. Patients who clinically improve with induction intravenous therapy and do not have CNS disease may be switched to oral monotherapy (usually after 3–6 weeks) based on susceptibility results. In immunocompromised patients, with CNS disease and/or multiorgan involvement, after a minimum six weeks of intravenous antibiotic therapy and clear evidence of clinical improvement, oral therapy with two susceptible drugs is recommended for maintenance therapy. Patients who are switched to oral therapy should be closely monitored to confirm a continued clinical response.

Our patients with pulmonary and cutaneous nocardiosis were treated with an induction regimen with renal-adjusted doses of imipenem and co-trimoxazole for 6 weeks followed by 6 months of maintenance therapy with co-trimoxazole. Minocycline was used in two patients who had co-trimoxazole-resistant nocardiosis and in one patient who was allergic to co-trimoxazole.

The optimal duration of antimicrobial treatment for severe disease has not been determined but usually requires treatment for 6–12 months for cutaneous and severe infection in immunocompromised patients. Serious pulmonary infection is treated for 6–12 months or longer.[15]

Patients with nocardiosis should be monitored for the response to therapy and possible drug toxicity. In addition, radiographic studies are useful to evaluate clinical improvement in patients with severe infection. It is advised to obtain follow-up imaging studies using chest radiographs and/or computed tomography (CT) scans for pulmonary disease and brain CT or magnetic resonance imaging scans for CNS disease. In our cohort, repeated radiologic studies were done at 6 and 12 months after clinical cure in our patients for confirmation.

Conclusions

Currently, there is no routine single serologic test available to detect patients with *Nocardia* infection. Initial cultures may yield negative results due to the slow growth of the organism and its variable colony morphology. Therefore, repeated specimens for culture should be obtained using aggressive approaches in suspected cases, such as bronchoscopic lavage and aspiration of abscesses. In our study, the majority of patients necessitated bronchoscopic lavage with Gram stain and culture, as initial sputum Gram stains and cultures were negative. In conclusion, maintaining a high index of suspicion and pursuing aggressive investigation for nocardiosis in

Table 1: Demographic features, clinical presentation, transplant details, methods of diagnosis, treatment, and outcomes of nocardiosis in renal allograft recipients

Age (years)	Sex	Live/ deceased	Induction	Maintenance IS	Timing of infection posttransplant	History of rejection within 6 months of infection	ART received	Clinical presentation
58	Male	LD	Basiliximab	P/T/MPA	2 months	Nil	Nil	LRTI
31	Male	LD	Basiliximab	P/T/MPA	2 months	Nil	Nil	LRTI
44	Male	LD	Basiliximab	P/T/MPA	6 months	Nil	Nil	LRTI
41	Male	LD	Basiliximab	P/T/MPA	9 months	Nil	Nil	LRTI
48	Female	DD	ATG	P/T/MPA	12 months	ACR	MP	LRTI
26	Male	LD	Basiliximab	P/T/MPA	24 months	ACR	MP	LRTI
45	Male	LD	Basiliximab	P/T/MPA	24 months	ACR	MP	LRTI
47	Male	LD	Basiliximab	P/T/MPA	24 months	ACR + ABMR	MP + PLEX + A TG/RTx	LRTI
52	Male	LD	Basiliximab	P/T/MPA	36 months	Nil	Nil	LRTI
31	Male	LD	No induction	P/CsA/AZA	36 months	Nil	Nil	LRTI
58	Male	LD	Basiliximab	P/CsA/AZA	48 months	Nil	Nil	LRTI
27	Male	LD	Basiliximab	P/CsA/AZA	60 months	Nil	Nil	LRTI
39	Male	LD	Basiliximab	P/T	84 months	Nil	Nil	LRTI
70	Male	LD	Basiliximab	P/T	96 months	Nil	Nil	LRTI
45	Female	LD	Basiliximab	P/T/MPA	2 months	Nil	Nil	Asymptomatic
50	Female	LD	Basiliximab	P/T/MPA	4 months	Nil	Nil	Asymptomatic
46	Male	LD	Basiliximab	P/T/AZA	60 months	Nil	Nil	Skin abscess
46	Male	LD	Basiliximab	P/T/AZA	72 months	Nil	Nil	Skin abscess
39	Male	LD	Basiliximab	P/T/AZA	72 month	Nil	Nil	Skin abscess
47	Male	LD	Basiliximab	P/T/AZA	10 years	Nil	Nil	Skin abscess
69	Male	LD	Basiliximab	P/T/AZA	10 years	Nil	Nil	Skin abscess
57	Male	DD	ATG	P/CsA/AZA	16 years	Nil	Nil	Skin abscess
50	Female	DD	ATG	P/T/MPA	22 years	Nil	Nil	Skin abscess
22	Male	LD	Basiliximab	P/T/MPA	5 months	ACR	MP	Fever/headache/ seizures
43	Male	LD	Basiliximab	P/T/MPA	15 months	ABMR	MP + PLEX + RTx	Fever/headache/ seizures
51	Male	LD	No induction	P/T/AZA	60 months	Nil	Nil	Graft tenderness

Age (years)	Diagnosis	Methods of diagnosis	Species isolated	Antibiogram		Treatment received		Mortality
				Carb	TS	Ind (6 weeks)	Mnt (6 months)	
58	Pulmonary	Sputum - c/s	-	S	S	Carb + TS	TS	-
31	Pulmonary	Sputum - c/s	-	S	S	Carb + TS	TS	-
44	Pulmonary	Sputum - c/s	-	S	S	Carb + TS	TS	-
41	Pulmonary	Sputum - c/s	Nc	S	S	Carb + TS	TS	-
48	Pulmonary	Sputum - c/s	Nc	S	S	Carb + TS	TS	-
26	Pulmonary	Sputum - c/s	-	S	S	Carb + TS	TS	Succumbed to illness after 2 months with sepsis
45	Pulmonary	Sputum - c/s	-	S	S	Carb + TS		
47	Pulmonary	Sputum - c/s	-	S	S	Carb + TS	TS	-
52	Pulmonary	BAL + TBLB	-	S	S	Carb + Mino	Mino	-
31	Pulmonary	BAL + TBLB	Nb	S	R	Carb + Mino	Mino	-
58	Pulmonary	BAL + TBLB	Nb	S	R	Carb + Mino	Mino	-
27	Pulmonary	BAL + TBLB	Nb	S	R	Carb + Mino	Mino	-
39	Pulmonary	CT-Lung Bx	-	S	S	Carb + TS	TS	-
70	Pulmonary	CT-Lung Bx	-	S	S	Carb + TS	TS	-
45	Pulmonary	BAL + TBLB	Nw	S	R	Carb + Mino	Mino	-
50	Pulmonary	BAL + TBLB	Na	S	S	Carb + TS	TS	-
46	Cutaneous	Pus - C/s	-	S	S	Carb + TS		
46	Cutaneous	Pus - C/s	-	S	S	Carb + TS	TS	
39	Cutaneous	Pus - C/s	Na	S	S	Carb + TS	TS	

Contd...

Table 1: Contd...

Age (years)	Diagnosis	Methods of diagnosis	Species isolated	Antibiogram		Treatment received		Mortality
				Carb	TS	Ind (6 weeks)	Mnt (6 months)	
47	Cutaneous	Pus - C/s	Na	S	S	Carb + TS	TS	
69	Cutaneous	Pus - C/s	Na	S	S	Carb + TS	TS	
57	Cutaneous	Pus - C/s	Na	S	S	Carb + TS	TS	
50	Cutaneous	Pus - C/s	Nf	S	S	Carb + TS	TS	
22	Disseminated	Bone marrow culture	-	S	S	Carb + TS	TS	
43	Disseminated	TBLB	-	S	S	Carb + TS	TS	
51	Graft abscess	Pus C/s	-	S	S	Carb + TS	TS	Succumbed to illness after 2 months with sepsis and DIC

ACR: Acute cellular rejection, ABMR: Antibody-mediated rejection, ART: Antirejection therapy, ATG: Antithymocyte globulin, AZA: Azathioprine, BAL: Bronchoalveolar lavage, Carb: Carbapenem, CT: Computed tomography, C/s: Culture and sensitivity, CsA: Cyclosporine, DIC: Disseminated intravascular coagulation, LRTI: Lower respiratory infection, - Prednisolone, MP: Methylprednisolone pulse, Mino: Minocycline, MPA: Mycophenolate acid, Globulin, RTx: Rituximab, S: Sensitive, R: Resistant, T: Tacrolimus, TBLB: Transbronchial lung biopsy, TS: Trimethoprim and sulfamethoxazole

Table 2: Antibiogram of *Nocardia*

Nocardia species	Number of cases ($n=26$) (%)	Sensitivity to co-trimoxazole	Sensitivity to carbapenems
Unidentified species	14 (53.8)	Sensitive	All isolates are sensitive
Nocardia asteroides	5 (19.2)	Sensitive	
Nocardia beijingensis	3 (11.5)	All isolates resistant	
Nocardia cyriacigeorgica	2 (7.69)	Sensitive	
Nocardia farcinica	1 (3.84)	Sensitive	
Nocardia wallacei	1 (3.84)	All isolates resistant	

renal allograft recipients can facilitate early diagnosis, enabling prompt and adequate treatment to prevent disease dissemination.

Research quality and ethics statement

This study was approved by the Institutional Review Board (vide minute number: 13641, dated December 2, 2020). The authors followed applicable EQUATOR Network guidelines during the conduct of this research project.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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