Nocardiosis in Renal Transplantation: Case Series from India

Abstract

Nocardiosis is a rare opportunistic infection seen in kidney transplant patients and is caused by aerobic actinomycete. Disease manifestations can vary from a localized infection to multisystem organ failure. In this retrospective case series, we present 16 cases of Nocardiosis. The median age of the patients was 44 years. The median time from transplant to nocardiosis was 21 months. Acute rejection episodes and CMV infection within 6 months of nocardiosis were found in 12.5% and 25%, respectively. The most common organ involvement was the lungs (75%), followed by the brain (12.5%). Only one patient showed cutaneous involvement (6.25%). Mean creatinine at presentation was 0.7 mg/dL (mean eGFR: 92 ± 27 mL/min/1.73 m^2). Trimethoprim/sulfamethoxazole resistance was found in 25% of patients. Five patients (31.25%) succumbed to the infection. Nocardiosis has a very low incidence but a high rate of mortality.

Keywords: *Infection, Nocardia, transplantation*

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Introduction

Nocardiosis is a rare opportunistic infection seen in immunocompromised patients, such as kidney transplant patients. It is ubiquitous in the environment, including in soil and organic matter. It is a slow-growing organism, thus causing delayed diagnosis and treatment. The clinical syndrome can vary and can affect the lungs, central nervous system (CNS), cutaneous tissues and can be disseminated, causing multi-organ failure. Lungs are the most commonly involved organs in immunosuppressed patients. Primary skin involvement (cutaneous nocardiosis) is more commonly seen in immunocompetent patients.[1] Disseminated and cerebral cases have a poor prognosis.[2] Trimethoprim/sulfamethoxazole (TMP-SMX) is given as prophylaxis in kidney transplant patients.[3] The mortality associated with nocardiosis in renal allograft recipients is 25%, but it increases by >2-fold in patients with CNS involvement.[4] Despite such high mortality, there are limited data on nocardiosis in kidney transplant patients because of the following factors: unfamiliarity with the disease, causing difficulty in diagnosis; nonspecific clinical presentation; and the presence of coinfections that preclude further workup for nocardiosis. Thus, we present a case series evaluating the clinical course, treatment response, and patient and graft outcomes in kidney transplant patients affected with nocardiosis.

Case Series

A total of 1801 kidney transplants were done from 2010 to 2019. Sixteen cases of nocardiosis were identified. Baseline features of patients are shown in Table 1. The most common clinical presentation was fever with cough (75%), with a mean duration of symptoms before admission of 6 ± 3 days. Other rare presentations included headache (25%), vomiting (19%), and skin lesions (6%). A history of CMV infection 6 ± 1.2 months prior to nocardiosis was found in 25% of patients. Two patients (12.5%) had a history of acute cellular rejection 3 and 2 months prior to Nocardia infection, respectively, which was treated with steroid pulse (total: 1.5 g) followed by an increase in the dose of immunosuppressive drugs. All patients had stable kidney function (creatinine <1 mg/dL).

The most common organ involvement was the lungs (75%), followed by the brain (12.5%). Only one patient showed cutaneous involvement (6.25%) [Table 2]. The severe form of the disease in the

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form of disseminated infection was seen in one patient. Subspecies identification was possible in the last 3 years of study after the introduction of MALDI TOF. Six patients were diagnosed with nocardiosis from 2017 to 2019, of which *Nocardia farcinica* was the most common type (4/6 patients) and was resistant to TMP-SMX. Patients were treated as per the sensitivity report with intravenous antibiotics initially followed by oral antibiotics. The lead time from the first appearance of symptoms till the start of the therapy was 12 ± 4 days. The mortality rate was 31.25%. Patients with brain involvement and disseminated infection had 100% mortality.

Table 1: Baseline characteristics of patients

Variable	Result
Age in years (Median, IQR)	44, 39.75-56.25
Gender (Male/Female)	14/2
Diabetes, *n* (%)	3 (18.75%)
Hypertension (*n*, %)	16, 100%
RAR duration in months (Median, IQR)	21, 9.75-45
H/O rejection before 6 months of infection (*n*, %)	2, 12.5
H/O CMV infection before 6 months of infection (*n*, %)	4, 25
Mean creatinine at presentation (mg/dL)	0.7
Mean eGFR at presentation	92±27 mL/min/1.73 m^2
Induction IS:	
Anti-thymocyte globulin (ATG) (*n*, %)	15, 93.75
ATG-Fresenius (*n*, %)	1, 6.25
Dose of ATG	3 mg/kg
Maintenance IS:	
Tacrolimus (*n*, %)	16, 100
Mycophenolate mofetil (MMF) (*n*, %)	16, 100
Prednisolone (*n*, %)	16, 100
Prednisolone dose (mg/dL), mean	5
Tacrolimus levels (ng/mL), mean	5.08
MMF dose (mg/dL), mean	1500
Trimethoprim/sulfamethoxazole prophylaxis	9, 56.25

Discussion

Nocardiosis is a rare infection that is caused by the Nocardia genus. Nocardia is gram-variable and weakly acid-fast bacilli in various suboptimal growth conditions. It may appear gram-negative and acid-fast-stain-negative with a longer incubation period for growth. Thus, a strong suspicion is needed for diagnosis.[2] The incidence of nocardiosis in solid organ transplant (SOT) recipients ranges from 0.6% to 2.65%.[5,6] Among SOT recipients, the highest incidence of nocardiosis is found in lung transplant patients.[6] The incidence of nocardiosis in kidney transplant patients varies from 0.7% to 2.6%.[7,8] Lungs are the most commonly involved organ in nocardiosis, as was found in our cases.[9]

Species identification is important as it guides treatment. After the introduction of MALDI-TOF at our center, six patients were diagnosed with nocardiosis, of which four were infected with *Nocardia farcinica*, one patient with *Nocardia wallacei*, and one with *Nocardia cyrigeorgica*. *Nocardia farcinica* is the most predominant species isolated in SOT patients;[6,10] similar findings were noted in our case series after the introduction of subspecies identification. *Nocardia farcinica* caused all pulmonary, disseminated, and brain infections. *Nocardia farcinica* was resistant to TMP-SMX, which used to be first-line therapy against nocardiosis before subspecies identification and sensitivity testing.

Table 2: Site of involvement, species, drug sensitivity, and outcomes of patients with nocardiosis

			Drug Sensitivity				Outcome
	Organ involved	Species	TMP-SMX	Linezolid	Imipenem	Amikacin	
1	Lungs	Nocardia	S	S	S	S	Recovered
2	Lungs	Nocardia	S	S	S	S	Recovered
3	Cutaneous	Nocardia	S	S	S	S	Recovered
4	Lungs	Nocardia	S	S	S	S	Death
5	Lungs	Nocardia	S	S	S	S	Recovered
6	Lungs	Nocardia	S	S	S	S	Recovered
7	Lungs	Nocardia	S	S	S	S	Death
8	Lungs	Nocardia	S	S	S	S	Recovered
9	Lungs	Nocardia	S	S	S	S	Recovered
10	Brain	Nocardia	S	S	S	S	Death
11	Lungs	Nocardia farcinica	R	-	S	S	Recovered
12	Brain	Nocardia farcinica	R	-	S	S	Death
13	Disseminated	Nocardia farcinica	R	-	S	S	Death
14	Lungs	Nocardia cyrigeorgica	S	-	S	S	Recovered
15	Lungs	Nocardia farcinica	R	S	S	S	Recovered
16	Lungs	Nocardia wallacei	S	-	R	R	Recovered

TMP-SMX: Trimethoprim-Sulfamethoxazole, R: Resistant, S: Sensitive

Immunosuppressive agents decrease both cellular and humoral immunity, thereby increasing the risk for nocardiosis. Calcineurin inhibitors (cyclosporine and tacrolimus) inhibit IL-2 production, thereby inhibiting T cell proliferation and cellular immunity. In addition, B cell immunity is indirectly affected due to impaired T cell functions.[11] Steroids affect both innate and adaptive immunity.[12] All of our patients were on steroids, mycophenolate mofetil, and tacrolimus. Moreover, all our patients had received an induction agent with ATG or ATG-Fresenius. Thus, intense immunosuppression increases the risk of opportunistic infection.

TMP-SMX prophylaxis has been in use in our center in most kidney transplant patients. Nine out of 16 patients had received TMP-SMX prophylaxis for 6 months. However, contrary to routine practice, some reports have suggested that TMP-SMX may not protect against nocardiosis.[10,13] Such association could not be analyzed in view of small sample size. However, nocardiosis did not occur when our patients were on TMP-SMX prophylaxis.

Association between CMV disease and nocardiosis is variable. CMV is an independent risk factor for nocardiosis,[14] and similar findings were found by Kürşat S *et al*.[9] and Peleg *et al*.,[13] while CMV viremia was not found as an independent risk factor for nocardia by Coussement *et al*.[10] In our case series, four patients had CMV infection within 6 months prior to nocardiosis. The treatment of choice for nocardiosis is TMP-SMX. It can be used in combination with the following drugs: imipenem, meropenem, linezolid, amikacin, fluoroquinolones, and minocycline.[15,16] Ideally, treatment should be based on a culture sensitivity report and using a combination of drugs for systemic illness.[4] Seven patients received a combination of imipenem and linezolid, five patients received a combination of imipenem and amikacin, and four patients received TMP-SMX alone.

Mortality was seen in five patients (31.25%), while 68.75% of patients recovered. Cerebral nocardiosis has a poor prognosis and is associated with increased mortality.[2] Similar findings were found in our case, with 100% mortality in cerebral nocardiosis.

Conclusion

Nocardiosis in kidney transplant patients has a very low incidence but is an important cause of mortality. *Nocardia farcinica* is the predominant species resistant to TMP-SMX. Cerebral and disseminated nocardiosis has a poor prognosis. Drug sensitivity is an important tool to guide treatment.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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Conflicts of interest

There are no conflicts of interest.

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