Nocardiosis In Kidney Transplant Patients: Two Cases of a Rare but Life-Threatening Disease and a Narrative Review of the Medical Literature

Nefrologo in corsia

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ABSTRACT

Nocardiosis is an uncommon but serious opportunistic bacterial infection caused by the genus *Nocardia*. Immunosuppression significantly increases the risk of infection, with an incidence of 0.4% to 3.6% in renal transplant patients. This disease primarily affects the lungs, skin, and central nervous system (CNS), but it can also disseminate to other parts of the body, significantly increasing the associated mortality. Although it can be challenging, early diagnosis is crucial, as it may be life-saving. The primary treatment for nocardiosis involves long-term antibiotic therapy. However, this treatment is often complicated by poor tolerance due to renal function impairment, requiring close monitoring and individualized treatment.

In this report, we present two cases of nocardiosis, highlighting the complexities of diagnosis and management in renal transplant patients.

KEYWORDS: nocardiosis, kidney transplant, antibiotic treatment, prognosis

Introduction

Nocardiosis is a rare but serious opportunistic infection caused by bacteria from the genus Nocardia. These bacteria are commonly found in the environment, particularly in soil and water. Although nocardiosis is relatively uncommon, patients who have undergone kidney transplants are at a higher risk due to their immunocompromised state, required to prevent rejection [1]. Indeed, several factors, such as kidney failure and prolonged high-dose corticosteroid use, can further impair the immune system and predispose patients to infections (Table 1) [2, 3].

Nocardiosis may manifest in various clinical forms. The infection often begins in the lungs, leading to pneumonia, which can cause symptoms such as cough, fever, and difficulty breathing. Nocardia can also spread to the central nervous system, resulting in brain abscesses. The infection can sometimes affect the skin, leading to sores or ulcers (cutaneous infections). In severe instances, nocardiosis can disseminate to multiple organs, potentially resulting in multisystem organ failure [4, 5].

Diagnosing nocardiosis can be challenging, especially in immunocompromised patients like those who have undergone kidney transplants. The symptoms are often nonspecific, and the bacteria grow slowly, which can delay obtaining a definitive diagnosis from microbiological testing. Standard routine cultures frequently fail to identify Nocardia because these bacteria require special media and conditions for growth [5].

The prognosis for nocardiosis in kidney transplant patients is often unfavorable, particularly in cases of dissaminated disease [2]. Hence, awareness of risk factors, early recognition of symptoms, and proper treatment are essential for improving patient outcomes.

This report discusses two cases of Nocardia infection in transplanted patients, detailing possible treatment options and the prognosis for this infection. The two cases illustrate how severe an opportunistic infection can be, often remaining asymptomatic until it spreads. A timely diagnosis can be lifesaving. This highlights the necessity of examining the critical elements of diagnosing and treating this rare infection in renal transplanted and immunosuppressed patients.

Immunosuppression	– HIV/AIDS (low CD4 count) – Organ transplantation (immunosuppressive therapy) – Chronic corticosteroid use – Chemotherapy for solid tumors – Use of biological agents (e.g., TNF inhibitors)
Chronic Lung Diseases	– Chronic obstructive pulmonary disease (COPD) – Cystic fibrosis – Pulmonary alveolar proteinosis – Bronchiectasis – History of previous lung infections or structural abnormalities
Hematologic malignancies	– leukemia – lymphoma
Skin Injuries	– Trauma or direct inoculation of Nocardia (e.g., gardening, farming)
Metabolic Disorders	– Diabetes mellitus – Chronic Kidney Disease (CKD) – Renal Replacement Therapy
Substance Use	– Alcoholism
Inherited Disorders	– Chronic granulomatous disease (CGD)
Other Factors	– Malnutrition

Table 1. Risk factors for Nocardiosis.

Case One: Mr. AA

The patient is a 70-year-old man with a history of kidney transplantation performed six years earlier. Induction therapy with basiliximab was followed by maintenance immunosuppression with cyclosporine, mycophenolate mofetil, and prednisone. Four years after transplantation, he developed chronic antibody-mediated rejection, C4d-negative, which was treated with intravenous corticosteroids. His immunosuppressive regimen was subsequently switched to tacrolimus (target trough levels 6-8 ng/mL), mycophenolate mofetil (500 mg twice daily), and prednisone (5 mg daily). Renal function progressively declined despite treatment, with the median eGFR reaching 45 mL/min/1.73m². The patient was initially hospitalized for community-acquired left lower lobe pneumonia, treated with Ceftriaxone and Levofloxacin for 5 days, followed by Levofloxacin alone for an additional 4 days, with apparent resolution. The following week, he was readmitted for a right pretibial skin lesion, which was drained and treated with antibiotics (amoxicillin-clavulanate for 5 days). Three weeks later, despite initially favorable progress, he consulted the emergency department for wound dehiscence, and antibiotic therapy was reinstated upon readmission. The next day, he presented to the emergency department with left facial palsy, left arm weakness and abnormal speech and was subsequently hospitalized. An MRI reveals an edematous right frontal/precentral cerebral lesion, highly suspected of being an abscess (Figure 1a). A thoracic scan shows pulmonary involvement in the form of parenchymal consolidation in the lingula with cranial extension and a nodular morphology, along with a ground-glass nodule in the same lobe (Figure 1b). The patient underwent neurosurgical evacuation of the cerebral abscess, and cultures revealed the growth of *Nocardia abscessus*, which was also isolated from cultures of the pretibial lesion. Thus, the diagnosis was disseminated *Nocardia* infection with cerebral involvement, interpreted as a pulmonary manifestation, with secondary skin and brain involvement. The patient was treated with combination therapy of ceftriaxone and sulfamethoxazole-trimethoprim for the first six weeks, followed by ceftriaxone alone (due to sulfamethoxazole-trimethoprim intolerance) for up to one year of overall treatment, with clinical and radiological evidence of complete recovery from the disease. Unfortunately, a few months after completing treatment, the patient died from respiratory failure due to severe SARS-CoV-2 infection complicated by ARDS and bacterial superinfection.

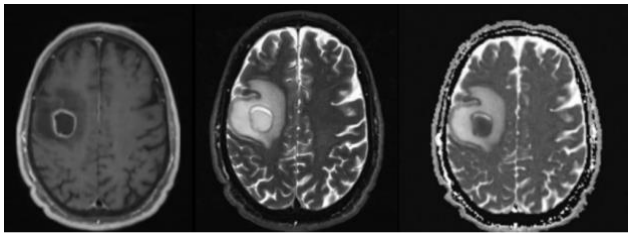

Figure 1a. The cerebral magnetic resonance imaging (MRI) shows a right frontal/precentral abscess.

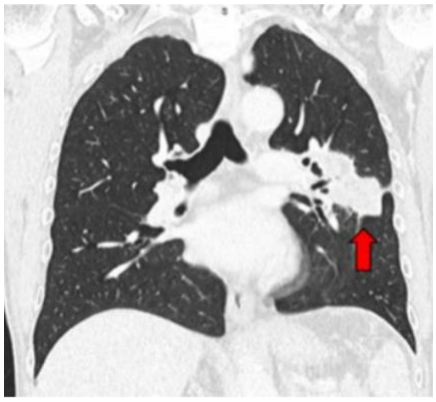

Figure 1b. The thoracic computed tomography (CT) scan reveals pulmonary involvement in the apical left lung (red arrow).

Case two: Mr. BB

The patient is a 57-year-old man who had undergone a double transplant (hepatic 5 years earlier for cirrhosis due to non-alcoholic fatty liver disease, and renal 5 months earlier for diabetic nephropathy). He was treated with anti-T-lymphocyte globulin (900 mg) as induction therapy and subsequently immunosuppressed with tacrolimus (target 6-8 ng/mL), mycophenolate mofetil (750 mg twice daily), and prednisolone 5 mg/day, while maintaining preserved renal function (eGFR 70 mL/min/1.73m²). He was initially hospitalized with suspected pneumonia of the left upper lobe, which was treated with piperacillin-tazobactam for 10 days, resulting in apparent full resolution. One month later, he was readmitted due to severe deconditioning. At that time, he reported progressive bilateral thigh pain, anorexia with weight loss, confusion; on examination, he presented with moderate clinical anasarca. A CT scan shows multifocal infiltrates in the lungs (Figure 2a) and bilateral dense-content collections in the thighs (Figure 2b). Nocardia farcinica is identified in blood culture, bronchial aspirate, bronchoalveolar lavage, muscular collections, and culture from a right knee arthrocentesis (late evidence of monoarthritis). Further investigations with a brain MRI reveal several small ring-enhanced lesions compatible with abscesses (not shown). The final diagnosis was disseminated nocardiosis involving blood, lungs, muscles, joints, and brain. Regrettably, the treatment process has proven to be more complex than the diagnosis. This is mainly due to an intolerance to Co-trimoxazole—the primary specific therapy—as well as to other treatments like Imipenem and Linezolid. The patient was hospitalized for over a month but was eventually discharged with a simplified treatment based on Ceftriaxone and Moxifloxacin. His condition gradually improved. Radiological follow-up at 6 months from the start of treatment showed complete resolution of the lesions. The patient continued therapy for a total of one year. At the 2-year follow-up, the patient remains in good health and is currently doing well.

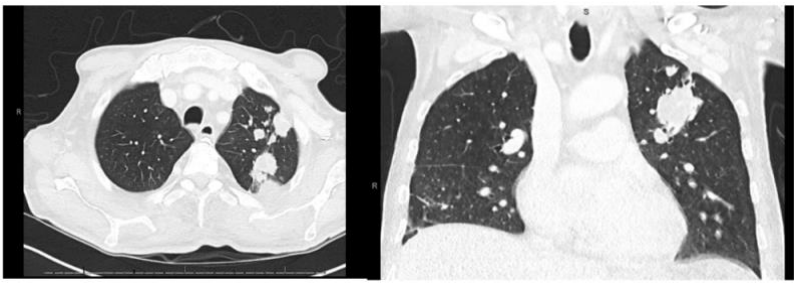

Figure 2a. The thoracic computed tomography (CT) scan shows multifocal infiltrates in the left lung.

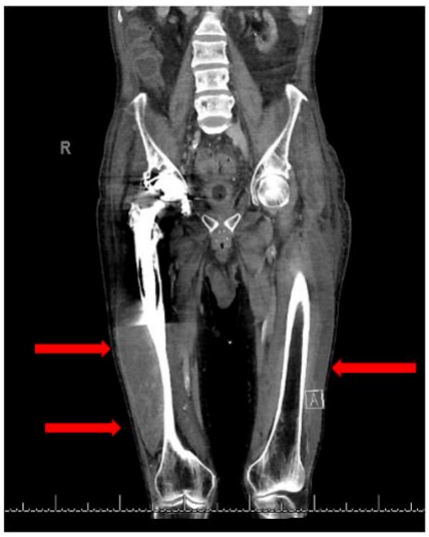

Figure 2b. The magnetic resonance imaging (MRI) shows bilateral dense-content collections in the thighs (red arrows).

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Discussion

Nocardia is a Gram-positive aerobic filamentous bacterium of the Actinomyces species commonly found in soil, water, and decaying vegetation. It is known to be an opportunistic pathogen that can cause infections, particularly in individuals with an impaired T-cell mediated response, such as immunocompromised patients, especially among solid organ transplant recipients (Table 1) [2].

Some lines of evidence suggest that the incidence of the disease is increasing, likely due to the growing number of transplant patients and the improved microbiological methods of detection [6, 7]. In renal transplanted patients, the reported incidence is 0.4-3.6% [2].

The disease can be acquired by inhaling bacteria present in the environment or through skin lesions. Nocardiosis can affect any body organ, but it most commonly affects the lungs, brain, and skin. In renal transplant patients, pulmonary involvement is the most common finding at the time of diagnosis, accounting for up to 88% of cases. At the same time, bacteremia is less frequent and is typically associated with catheter use [4].

Infections typically develop within two months to two years after transplantation. Known risk factors are related to the transplant itself, including the patient's age at the time of surgery, history of rejection or failure, deceased donor transplantation, as well as the administration of immunosuppressive drugs such as basiliximab, cyclosporine, tacrolimus, thymoglobulin, and, above all, corticosteroids [1, 3].

Diagnosing nocardiosis can be challenging due to nonspecific clinical manifestations and the slow growth of the bacteria in culture. Diagnosis is based on identifying bacteria in tissue or body fluid samples. Culture on selective media is the gold standard diagnostic method; however, culture may take up to two weeks to yield results. As a result, diagnosis might be postponed, while PCR can speed up identification of the germ [5].

Due to its indolent course, the infection may be discovered when the disease has already disseminated (involvement of ≥2 non-contiguous organs; typical locations include, as previously mentioned, the brain, skin, lungs, but also bones, eyes, joints, and kidneys). When disseminated, mortality among renal transplant patients demonstrates a significant increase, approaching one in two affected individuals (50-60% vs. 15-20%) [1].

Radiological studies, such as computed tomography (CT) or magnetic resonance imaging (MRI), can aid in the diagnosis of pulmonary or central nervous system (CNS) nocardiosis, even though they are not specific. CNS nocardiosis is frequently observed in immunocompromised patients (up to 80%); however, it can be asymptomatic, and if undetected, it may lead to treatment failure. Therefore, the role of cerebral imaging in asymptomatic patients is still discussed [8, 9]. However, radiological studies may help assess the response to therapy.

Even after diagnosis, treating nocardiosis in renal transplant patients proves difficult due to possible interactions between antibiotics and immunosuppressants, which can increase toxicity, along with elevated rates of graft failure rejection. The treatment involves long-term appropriate antimicrobial therapy and drainage/debridement of the abscesses.

The mainstay of antibiotic therapy is sulfamethoxazole-trimethoprim (TMP-SMX), which demonstrates antimicrobial activity against most types of nocardial infections and can attain high tissue concentrations in the more frequently affected organs, such as the lungs, brain, skin, and bone. It is used for mild forms (even alone, for 3-6 months) or severe forms (higher dosage, usually associated with a second agent, up to one year) [9, 10].

Linezolid, which also shows excellent efficacy, is a second choice because of its well-known side

effects [9]. Other second-line antibiotics utilized for maintenance therapy, either in combination or as monotherapy, encompass Amikacin, Imipenem, Ceftriaxone, Cefotaxime, and Ciprofloxacin Minocycline [9, 10]. This antibiotic strategy shows a variable success rate, dependent on patient's underlying disease and site and extent of infection with a mean mortality rate at 26% [10].

When determining treatment, considering potential complications from antibiotic options is crucial, especially for transplant recipients with impaired renal function.

TMP-SMX is a sensible option as effective as Linezolid; it is administered orally, yet its tolerability is not guaranteed. It is known to potentially cause acute kidney injury, resulting from interstitial nephritis and acute tubular damage due to crystal deposition [11, 12]. Alternatively, in some cases, an artefactual effect of increased creatinine levels occurs even without a decline in glomerular filtration rate. This is attributed to the inhibition of a cationic transporter in the proximal convoluted tubule that handles creatinine secretion [13]. Furthermore, significant electrolyte imbalances, like hyponatremia and hyperkalemia, may arise, which may persist until treatment is discontinued, as seen in Case 2.

Linezolid, although highly effective and not nephrotoxic (with good oral bioavailability and CNS penetration), is known to cause myelo- and neurotoxicity. This effect is exacerbated in transplant patients due to the associated immunosuppressive therapy, which is time-dependent. For this reason, its use in nocardiosis is limited to initial empirical therapy or as a second-line option for patients who cannot tolerate TMP-SMX or other first-line agents [14].

Regarding other treatments, aminoglycosides, such as Amikacin, are known for their nephrotoxic effects. Approximately 25% of patients receiving this medication experience these effects, with an even higher rate among those with pre-existing renal impairment. This toxicity arises through three primary mechanisms: tubular toxicity, decreased glomerular filtration, and reduced blood flow [15].

Imipenem is usually well-tolerated in transplant patients; however, it can lead to myelotoxicity, especially thrombocytopenia and leukopenia, along with neurotoxicity. Thus, careful monitoring of patients during treatment is crucial [16].

Consequently, any treatment approach for Nocardiosis should be tailored and closely monitored for each individual patient.

Patients with a Nocardia infection experience higher rates of graft failure (67% vs. 43%) and kidney rejection (61% vs. 27%). Risk factors associated with graft rejection and failure include the use of anti-thymocyte globulin, chronic obstructive pulmonary disease, and central nervous system involvement such as brain abscess. Interestingly, a prior history of graft failure or rejection may appear to be protective. While this could reflect a selection bias inherent in observational studies, a plausible explanation is that clinicians tend to be more cautious in reducing immunosuppression in these patients – even in the setting of severe infection – due to the known risk of further rejection. Alternatively, the use of antibiotic prophylaxis with TMP-SMX may be different in subjects with a prior history of graft rejection. As a result, rejection recurrence or graft loss may be mitigated in infected subjects [2].

There is no agreement on how to reduce immunosuppression in the case of Nocardia infection, which should be considered to treat the disease effectively but poses risks of transplant rejection and immune reconstitution inflammatory syndrome, as observed in CNS cases infection [10, 17].

Preventing nocardiosis can be challenging due to the ubiquitous nature of the bacteria in the environment. However, individuals with compromised immune systems should avoid exposure to soil and other sources of the bacteria. Good hygiene practices, such as handwashing, can also help prevent the spread of the bacteria nocardiosis [18]. However, recent studies suggest that anti-

pneumocystis prophylaxis could reduce the risk of Nocardia infection in transplanted patients. Notably, infections during prophylaxis are still susceptible to TMP-SMX [19].

In summary, nocardiosis is a rare but potentially life-threatening infection that can affect any organ of the body. Renal transplant recipients are at an increased risk of nocardiosis due to the use of immunosuppressive drugs. Diagnosis can be challenging, but early recognition and treatment are essential for a good outcome. Treatment is equally complex, requiring a careful balance between effective antimicrobial therapy, the management of side effects and potential interactions with immunosuppressants. Prevention of nocardiosis can be challenging, but avoiding exposure to soil, practicing good hygiene and considering prophylactic strategies can help reduce the risk of infection.

BIBLIOGRAPHY

1. Coussement J, Lebeaux D, van Delden C, Guillot H, Freund R, Marbus S, et al. Nocardia infection in solid organ transplant recipients: a multicenter European case-control study. Clin Infect Dis 2016;63:338e45. https://doi.org/10.1093/cid/ciw241.
2. Gibson M, Yang N, Waller JL, Young L, Bollag WB, Kheda M, Mohammed A, Baer SL. Nocardiosis in renal transplant patients. J Investig Med. 2022 Jan;70(1):36-45. https:/doi.org/10.1136/jim-2021-001783. Epub 2021 Aug 23. PMID: 34426458.
3. Margalit I, Goldberg E, Ben Ari Y, Ben-Zvi H, Shostak Y, Krause I, Muhsen K. Clinical correlates of nocardiosis. Sci Rep. 2020 Aug 31;10(1):14272. https:/doi.org/10.1038/s41598-020-71214-4. PMID: 32868850; PMCID: PMC7459281
4. Williams E, Jenney AW, Spelman DW. Nocardia bacteremia: A single-center retrospective review and a systematic review of the literature. Int J Infect Dis. 2020;92:197-207. https://doi.org/10.1016/j.ijid.2020.01.011.
5. Duggal SD, Chugh TD. Nocardiosis: A Neglected Disease. Med Princ Pract. 2020;29(6):514-523. https:/doi.org/10.1159/000508717. Epub 2020 May 18. PMID: 32422637; PMCID: PMC7768126
6. Ambrosioni J, Lew D, Garbino J. Nocardiosis: updated clinical review and experience at a tertiary center. Infection. 2010 Apr;38(2):89-97. https:/doi.org/10.1007/s15010-009-9193-9. Epub 2010 Mar 20. PMID: 20306281.
7. Fatahi-Bafghi M. Nocardiosis from 1888 to 2017. Microb Pathog. 2018 Jan;114:369–84. https://doi.org/10.1016/j.micpath.2017.11.012.
8. Bargehr J, Flors L, Leiva-Salinas C, Flohr TR, Sawyer R, Bonatti H, Hagspiel KD. Nocardiosis in solid-organ transplant recipients: spectrum of imaging findings. Clin Radiol. 2013 May;68(5):e266-71. https:/doi.org/10.1016/j.crad.2012.11.021. Epub 2013 Jan 23. PMID: 23351777; PMCID: PMC3816150.
9. Margalit I, Lebeaux D, Tishler O, Goldberg E, Bishara J, Yahav D, Coussement J. How do I manage nocardiosis? Clin Microbiol Infect. 2021 Apr;27(4):550-558. https:/doi.org/10.1016/j.cmi.2020.12.019. Epub 2021 Jan 5. PMID: 33418019.
10. Restrepo A, Clark NM. Infectious Diseases Community of Practice of the American Society of Transplantation. Nocardia infections in solid organ transplantation: guidelines from the Infectious Diseases Community of Practice of the American Society of Transplantation. Clin Transplant. 2019;33(9): e13509. https:/doi.org/10.1111/ctr.13509.
11. Nucera G, Raffaelli V, Caliari L, Cantoni G, Marino P. Trimethoprim/sulfamethoxazole-induced acute renal failure: A case report. J Health Soc Sci. 2017;2(2):215-220.
12. Fraser TN, Avellaneda AA, Graviss EA, Musher DM. Acute kidney injury associated with trimethoprim/sulfamethoxazole. J Antimicrob Chemother. 2012 May;67(5):1271-7. https:/doi.org/10.1093/jac/dks030. Epub 2012 Feb 20. PMID: 22351681.
13. Berglund F, Killander J, Pompeius R. Effect of trimethoprim-sulfamethoxazole on the renal excretion of creatinine in man. J Urol. 1975 Dec;114(6):802-8. https:/doi.org/10.1016/s0022-5347(17)67149-0. PMID: 1195454.
14. De La Cruz O, Minces LR, Silveira FP. Experience with linezolid for the treatment of nocardiosis in organ transplant recipients. J Infect. 2015 Jan;70(1):44-51. https:/doi.org/10.1016/j.jinf.2014.08.010. Epub 2014 Aug 30. PMID: 25179664.
15. Wargo KA, Edwards JD. Aminoglycoside-Induced Nephrotoxicity. Journal of Pharmacy Practice. 2014;27(6):573-577. https:/doi.org/10.1177/0897190014546836.
16. Norrby SR. Neurotoxicity of carbapenem antibacterials. Drug Saf. 1996 Aug;15(2):87-90. https:/doi.org/10.2165/00002018-199615020-00001. PMID: 8884160.
17. Soman R, Koparkar V, Almeida A, Shetty A, Rodrigues C. Paradoxical Response in Cerebral Nocardiosis in a Renal Transplant Recipient. J Assoc Physicians India. 2018 Sep;66(9):91-92. PMID: 31321940.
18. Centers for Disease Control and Prevention (CDC) (2018). Nocardia
19. Passerini M, Nayfeh T, Yetmar ZA, Coussement J, Goodlet KJ, Lebeaux D, Gori A, Mahmood M, Temesgen Z, Murad MH. Trimethoprim-sulfamethoxazole significantly reduces the risk of nocardiosis in solid organ transplant recipients: systematic review and individual patient data meta-analysis. Clin Microbiol Infect. 2024 Feb;30(2):170-177. https:/doi.org/10.1016/j.cmi.2023.10.008. Epub 2023 Oct 19. PMID: 37865337.