Disseminated Nocardiosis in Kidney Transplant Recipients: A Report of 2 Cases

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Nocardiosis is a rare, life-threatening opportunistic infection caused by bacteria in the environment that predominantly affects immunocompromised patients. Nocardiosis most commonly involves the lungs but can disseminate to other organs. Disseminated nocardiosis, defined as *Nocardia* infection involving 2 or more organ systems, requires early detection and treatment because of high morbidity and mortality. We report 2 cases of disseminated nocardiosis with pulmonary and central nervous system involvement in kidney transplant recipients. Nocardiosis should be suspected in immunocompromised patients with fever and lung mass, although atypical presentations involving almost any organ can be seen. Solid organ transplant recipients are at greatest risk for *Nocardia* infection within the first 1 to 2 years after transplantation. However, the patients presented here developed disseminated nocardiosis several years after transplantation, which has important implications. Nocardiosis is treated with 2 to 6 weeks of empiric induction antibiotics, followed by 6 to 12 months of maintenance antibiotics based on antimicrobial susceptibility testing.

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INTRODUCTION

Nocardiosis is a rare opportunistic infection caused by the filamentous gram-positive *Nocardia* bacteria.[1] *Nocardia* species are pervasive in the soil and environment and infect individuals with weakened or dysfunctional immune systems.[2] Inhalation is the most common route of entry of *Nocardia* species, but ingestion and direct inoculation through the skin also occur.[3] Nocardiosis most commonly involves the lungs but can disseminate to other organs through contiguous or hematogenous spread. Patients with kidney transplants have the lowest *Nocardia* infection rate compared to patients with other solid organ transplants.[4,5] In a separate review of 5,126 solid organ transplant recipients, *Nocardia* infection was reported in 0.2% of kidney transplant recipients.[5] We report 2 cases of disseminated nocardiosis after kidney transplantation.

CASE REPORTS

Case 1

Patient 1 was a man in his 50s with kidney failure secondary to hypertension and reduced kidney mass from a right radical nephrectomy for renal cell carcinoma. He underwent a deceased donor kidney transplant 3 years before, with an uneventful posttransplant course. He received induction immunosuppression with alemtuzumab and solumedrol. There were no episodes of rejection. Maintenance immunosuppression included tacrolimus (2 mg twice daily), mycophenolate mofetil (1,000 mg twice daily), and prednisone (5 mg daily). He also received sulfamethoxazole-trimethoprim for *Pneumocystis* pneumonia prophylaxis and valganciclovir for cytomegalovirus prophylaxis after transplantation, but these were both discontinued due to recurrent leukopenia 2 months after.

He presented to the orthopedic clinic with a 10-day history of pain and swelling of the right shoulder. On presentation, he was febrile to 100.6°F but otherwise hemodynamically stable. Physical examination was notable for a soft tissue mass of the right scapula, and he was given symptomatic therapies for a right parascapular muscle tear. Computed tomography scan of the chest demonstrated a right upper lobe pulmonary nodule with satellite lesions. Positron emission tomography/computed tomography scan showed a large, partially necrotic, intensely fluorodeoxyglucose-avid mass in the soft tissues inferior to the right scapula and multiple masses in the lungs, brain, and cecum.

The differential diagnosis included osteosarcoma, chondrosarcoma, bronchogenic carcinoma, lymphoma, or granulomatous infection caused by *Mycobacterium tuberculosis*, nontuberculous mycobacteria, or *Nocardia*. Multiple tumor markers were negative. A core tissue biopsy from the right scapular mass was performed. The tissue sample culture was negative for acid-fast bacilli but demonstrated gram-positive beaded rods identified as *N pneumoniae*.

The patient received induction antimicrobial therapy with intravenous meropenem (2 g every 12 hours) and intravenous sulfamethoxazole-trimethoprim (160 mg every 8 hours) but changed to intravenous ceftriaxone (2 g every 12 hours) and oral sulfamethoxazole-trimethoprim (800-160 mg every 8 hours). A follow-up magnetic resonance imaging study without contrast of the brain 2 months after diagnosis demonstrated marked improvement in all lesions (Fig 1), and he was transitioned to maintenance antimicrobial therapy with oral doxycycline (100 mg twice daily) to complete 12 months of definitive treatment based on antimicrobial susceptibility testing. For his maintenance immunosuppression, mycophenolate mofetil was stopped, and he was maintained on tacrolimus and prednisone.

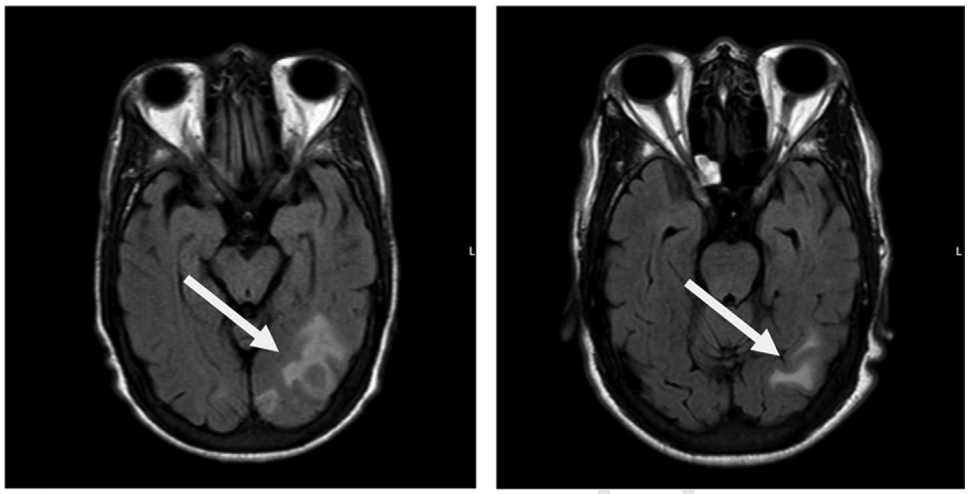

Figure 1. Patient 1, T2-weighted fluid-attenuated inversion recovery magnetic resonance imaging of the brain from before (left) and after 2 months of induction antibiotic therapy (right) for *Nocardia pneumoniae* (solid arrows).

Case 2

Patient 2 was a woman in her 70s with kidney failure secondary to focal segmental glomerular sclerosis who underwent a deceased donor kidney transplant a decade prior. She underwent induction immunosuppression with alemtuzumab and solumedrol, and she received sulfamethoxazole-trimethoprim *Pneumocystis* pneumonia prophylaxis and valganciclovir cytomegalovirus prophylaxis for 6 months after transplantation. Her posttransplant course was complicated by 2 episodes of acute cellular rejection treated with steroids within the first 2 years after transplant. She was maintained on immunosuppression with tacrolimus (1 mg twice daily), mycophenolic acid (360 mg twice daily), and sirolimus (0.5 mg every other day) thereafter with serum creatinine ranging between 1.6-1.8 mg/dL; however, sirolimus was changed to prednisone (5 mg daily) after surgery 6 months before presentation. Presenting symptoms included 3 days of headache and left upper extremity weakness and tingling. She was hemodynamically stable. Physical examination was notable for lethargy and focal numbness and weakness of the left upper extremity. Computed tomography scan without contrast of the chest demonstrated a right apical lung mass. Magnetic resonance imaging of the brain without contrast demonstrated distinct right frontal, right parieto-occipital, and left occipital lobe masses with surrounding edema.

The differential diagnosis included primary bronchogenic carcinoma with Pancoast syndrome, lymphoma, invasive mediastinal tumor, or granulomatous infection caused by *M tuberculosis*, nontuberculous mycobacteria, or *Nocardia*. Bronchoscopy with bronchoalveolar lavage and transbronchial needle aspiration of the right apical lung mass was performed. The cytology was negative for malignancy, but the tissue sample culture was positive for *N nova*.

She received induction antimicrobial therapy with intravenous imipenem-cilastatin (500 mg every 12 hours), oral linezolid (600 mg every 12 hours), and intravenous sulfamethoxazole-trimethoprim (192 mg every 8 hours). The imipenem-cilastatin was changed to meropenem (1,000 mg every 12 hours) because of seizures, and the linezolid was discontinued because of thrombocytopenia. For maintenance immunosuppression, mycophenolate mofetil was discontinued, and she was maintained on tacrolimus and prednisone. Follow-up magnetic resonance imaging without contrast of the brain 6 weeks after diagnosis demonstrated decreased size of the intracranial lesions (Fig 2), and she was transitioned to maintenance antimicrobial therapy with oral sulfamethoxazole-trimethoprim (800-160 mg twice daily) to complete at least 12 months of definitive treatment based on antimicrobial susceptibility testing. She subsequently died of complications of coronavirus disease 2019.

DISCUSSION

Nocardia species are ubiquitous gram-positive bacteria found in the soil and aquatic environments and have several modes of entry to humans. Because the host response against *Nocardia* is primarily T-cell mediated, nocardiosis may be seen in patients on chronic glucocorticoids or those with human immunodeficiency virus, malignancy, or hematopoietic stem cell or solid organ transplantation.[6] More cases of nocardiosis are being reported because of improved microbiological methods of detection and rising numbers of immunosuppressed patients.[7] In solid organ transplant recipients, the reported incidence of nocardiosis varies from 0.7% to 3.5%. Although less common, kidney transplant recipients may present with severe and disseminated *Nocardia* infection. Of over 50 *Nocardia* species known to cause disease in humans, the 3 commonly reported species causing nocardiosis among solid organ transplant recipients are *N nova*, *N farcinica*, and *N cyriacigeorgica*.[8,9] Based on our literature review,

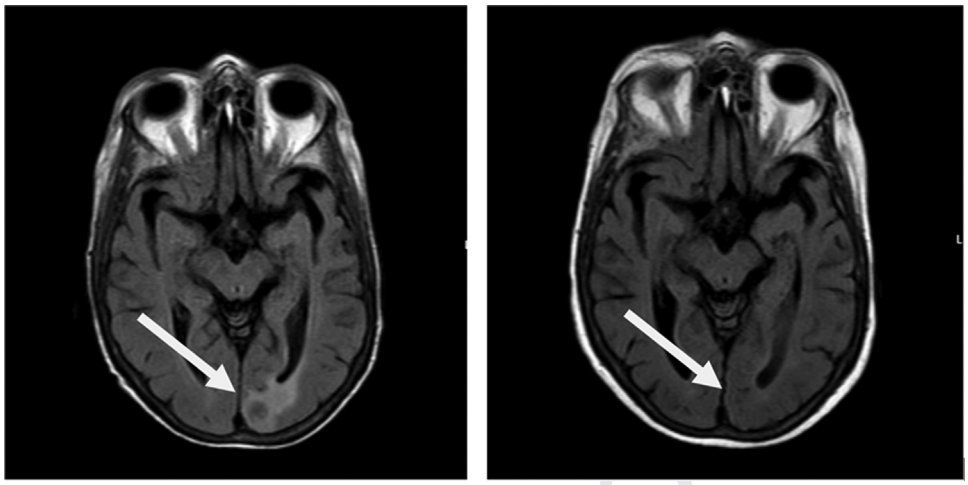

Figure 2. Patient 2, T2-weighted fluid-attenuated inversion recovery magnetic resonance imaging of the brain from before (left) and after 6 weeks of induction antibiotics (right) for *Nocardia nova* (solid arrows).

we have reported the first case of nocardiosis by *N pneumonie* in a kidney transplant recipient.

Disseminated nocardiosis, defined as *Nocardia* infection involving 2 or more organ systems, occurs through hematogenous or contiguous spread. The most frequently involved organs are lung, brain, skin, and subcutaneous tissue.[10] Some studies suggest that 88% of kidney transplant recipients who develop nocardiosis will present with pulmonary involvement and may have a high rate of disseminated disease.[8,11] Thus, early and accurate diagnosis is important because nocardiosis symptoms overlap with other disease entities, such as malignancy or other atypical infections (Box 1). Better prognosis is associated with earlier diagnosis and proper duration of antibiotic therapy.[5]

The risk of infection after solid organ transplant is associated with the state of immunosuppression, which may be related to the time since transplantation, episodes of rejection, and changes to the immunosuppression regimen. Modulating immunosuppression after diagnosis of *Nocardia* should be considered on a case-by-case basis, as antibiotic therapies are highly effective treatment for most patients with nocardiosis regardless of the concurrent immunosuppressive regimen. Nocardiosis often occurs within the first 1 to 2 years after solid organ transplantation, which is likely related to the higher levels of immunosuppression used in the early posttransplantation period. Yu et al[12] reported clinical characteristics of 66 cases of nocardiosis in kidney transplant recipients. Mean interval of onset of infection after transplant was 34.41 months.[5,13] Coussement et al[9] conducted a retrospective case-control study of adult patients diagnosed with nocardiosis after solid organ transplant in 36 European centers to determine risk factors for developing nocardiosis. In this multicenter European study of 117 patients receiving short-course antibiotics for the treatment of nocardiosis, solid organ transplant recipients demonstrated a 10-fold higher 1-year mortality compared with those without transplantation. The study also reported that high calcineurin inhibitor trough levels in the month before diagnosis, use of tacrolimus and corticosteroids at the time of diagnosis, and length of stay in the intensive care unit after solid organ transplant were independently associated with the development of nocardiosis.

The cases presented here add to the increasing number of reports of nocardiosis occurring much later in the posttransplantation course. Both patients presented here received maintenance immunosuppression with steroids and calcineurin inhibitors and presented with *Nocardia* infection 3 years and 1 decade after kidney transplantation. For patient 1, the premature discontinuation of sulfamethoxazole-trimethoprim because of leukopenia may have increased the risk of *Nocardia* colonization. For patient 2, there were 2 episodes of acute cellular rejection leading to augmentation of her immunosuppressive

Box 1. Teaching Points

- Nocardiosis is an uncommon opportunistic infection that can be life-threatening.
- Solid organ transplant recipients are at increased risk for nocardiosis, usually within the first 1 to 2 years after transplantation but potentially many years later.
- The differential diagnosis for nocardiosis includes other infectious organisms, abscesses, and malignancy.
- *Nocardia* are filamentous gram-positive bacteria that may cause localized infection or disseminated suppurative disease.
- Over 50 *Nocardia* species are known to infect humans.
- Treatment consists of 3 to 6 weeks of intravenous induction antibiotics followed by 6 to 12 months of maintenance antibiotics based on antimicrobial susceptibility.

regimen, which may have increased the risk of opportunistic infection years later. Further research is needed to better understand risk factors for nocardiosis, particularly for patients who may develop nocardiosis much later in the posttransplantation course.

Antibiotics are effective in most cases of nocardiosis. Generally, induction therapy with empiric antibiotics should be initiated for 2 to 6 weeks and then transitioned to targeted maintenance therapy with oral antibiotics for 6 to 12 months. However, there is no consensus on the most effective antibiotic approach and no clinical trials comparing antibiotic regimens. Choice and duration of therapy are based on antibiotic susceptibility testing and considerations relating to the site and extent of infection. Sulfamethoxazole-trimethoprim has antimicrobial activity against most nocardial infections and achieves high tissue concentrations in the lung, brain, skin, and bone.[2] Linezolid has potential as a second-line agent for antibiotic-resistant *Nocardia* species. In infections that involve the central nervous system, imipenem or amikacin are sometimes added as adjunctive antibiotic therapies.[14] In most cases, treatment for 6 months after clinical improvement is sufficient, but treatment for 12 months or longer may be required in severe and disseminated cases.[10,15,16] For example, in patients where nocardiosis has spread to the central nervous system, antibiotic therapy is continued for a year or longer based on clinical and imaging response.[7] There is also no consensus regarding the use of prophylactic antibiotics to prevent nocardiosis after solid organ transplantation. Sulfamethoxazole-trimethoprim is usually prescribed as prophylaxis for *P jiroveci* infection, but the specific dose and duration to prevent nocardiosis in solid organ transplant recipients is unknown. Although the use of prophylactic sulfamethoxazole-trimethoprim is associated with decreased incidence of *Nocardia* infections in solid organ transplant recipients, breakthrough cases of nocardiosis have been reported on daily and intermittent dosing.[4,5,14]

In conclusion, nocardiosis is a rare opportunistic infection that primarily affects patients with weakened immune systems, including solid organ transplant recipients. Kidney transplant recipients have the potential for severe and disseminated *Nocardia* infection. Nocardiosis should be suspected in immunocompromised patients with fever and lung mass, although atypical presentations are common, and almost any organ can be involved. Although most cases of nocardiosis occur within 1 to 2 years after transplantation, the cases presented here add to the increasing number of reports of *Nocardia* infection occurring much later in the posttransplant course. In most cases, *Nocardia* can be treated successfully with targeted antibiotic therapy.

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REFERENCES:

1. Brown-Elliott BA, Brown JM, Conville PS, Wallace RJ Jr. Clinical and laboratory features of the Nocardia spp. based on current molecular taxonomy. *Clin Microbiol Rev*. 2006;19(2):259-282. doi:10.1128/cmr.19.2.259-282.2006
2. 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. doi:10.1111/ctr.13509
3. Beaman BL, Beaman L. Nocardia species: host-parasite relationships. *Clin Microbiol Rev*. 1994;7(2):213-264. doi:10.1128/cmr.7.2.213
4. Shrestha S, Kanellis J, Korman T, et al. Different faces of Nocardia infection in renal transplant recipients. *Nephrology (Carlton)*. 2016;21(3):254-260. doi:10.1111/nep.12585
5. Peleg AY, Husain S, Qureshi ZA, et al. Risk factors, clinical characteristics, and outcome of Nocardia infection in organ transplant recipients: a matched case-control study. *Clin Infect Dis*. 2007;44(10):1307-1314. doi:10.1086/514340
6. Deem RL, Doughty FA, Beaman BL. Immunologically specific direct T lymphocyte-mediated killing of Nocardia asteroides. *J Immunol*. 1983;130(5):2401-2406.
7. Ambrosioni J, Lew D, Garbino J. Nocardiosis: updated clinical review and experience at a tertiary center. *Infection*. 2010;38(2):89-97. doi:10.1007/s15010-009-9193-9
8. Majeed A, Beatty N, Iftikhar A, et al. A 20-year experience with nocardiosis in solid organ transplant (SOT) recipients in the Southwestern United States: a single-center study. *Transpl Infect Dis*. 2018;20(4):e12904. doi:10.1111/tid.12904
9. Coussement J, Lebeaux D, van Delden C, et al. Nocardia infection in solid organ transplant recipients: a multicenter European case-control study. *Clin Infect Dis*. 2016;63(3):338-345. doi:10.1093/cid/ciw241
10. Lederman ER, Crum NF. A case series and focused review of nocardiosis: clinical and microbiologic aspects. *Medicine (Baltimore)*. 2004;83(5):300-313. doi:10.1097/01.md.0000141100.30871.39
11. Wilson JP, Turner HR, Kirchner KA, Chapman SW. Nocardial infections in renal transplant recipients. *Medicine (Baltimore)*. 1989;68(1):38-57. doi:10.1097/00005792-198901000-00003

12. Yu X, Han F, Wu J, et al. Nocardia infection in kidney transplant recipients: case report and analysis of 66 published cases. *Transpl Infect Dis*. 2011;13(4):385-391. doi:10.1111/j.1399-3062.2011.00607.x
13. Santos M, Gil-Brusola A, Morales P. Infection by Nocardia in solid organ transplantation: thirty years of experience. *Transplant Proc*. 2011;43(6):2141-2144. doi:10.1016/j.transproceed.2011.06.065
14. Clark NM, Reid GE; AST Infectious Diseases Community of Practice. Nocardia infections in solid organ transplantation. *Am J Transplant*. 2013;13(suppl 4):83-92. doi:10.1111/ajt.12102
15. John GT, Shankar V, Abraham AM, Mathews MS, Thomas PP, Jacob CK. Nocardiosis in tropical renal transplant recipients. *Clin Transplant*. 2002;16(4):285-289. doi:10.1034/j.1399-0012.2002.01145.x
16. Arduino RC, Johnson PC, Miranda AG. Nocardiosis in renal transplant recipients undergoing immunosuppression with cyclosporine. *Clin Infect Dis*. 1993;16(4):505-512. doi:10.1093/clind/16.4.505