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Nocardia infection in lung transplant recipients

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Abstract

Nocardia is a well-recognized pathogen in immunocompromised hosts, but the incidence of Nocardia infections in lung transplant recipients is not well defined. A chart review from 1990 to 2007 at Clarian Hospital Lung Transplant Center and Indiana University Medical Center revealed Nocardia infections in four of 410 lung transplant recipients despite prophylaxis. All infections were confined to lung and occurred at a median time of 315 d after transplantation. *Nocardia nova* was isolated in two patients, *Nocardia farcinica* in one, and unspecified *Nocardia* sp. in one. Nocardia isolates were susceptible to trimethoprim sulfa (TMP/SMX). Our data suggest that the dose of TMP/SMX, commonly used for Pneumocystis prophylaxis is not protective for Nocardia. Contrary to historic data reporting 40% mortality, none of the patients in our study died because of Nocardia. Nocardia infection is an under-recognized entity in lung transplant recipients, and the optimal duration of therapy and prophylaxis are unclear.

Keywords

immunocompromised host; Nocardia; transplantation

Nocardia sp. were first discovered in 1888 by Edmin Nocard and were recognized as human pathogens in 1891. Nocardia, an aerobic actinomycete, is capable of causing either a localized or disseminated infection in both immunocompetent and immunocompromised hosts. The hallmark of Nocardia infection is the diversity of its clinical manifestations with involvement of lungs, central nervous system, skin, and other organs. In the immunocompromised population, the species are increasingly recognized to complicate the course of solid organ transplantation (1). The incidence of nocardiosis in the United States has been estimated to be approximately 500–1000 new cases per year, of which 13% are transplant recipients (2).

The frequency of Nocardia infection in solid organ transplant patients varies from study to study. In a study from Italy, 23% of Nocardia cases were in recipients of organ transplantation (3). The data on Nocardia infections in lung transplants are sparse and the majority of cases have been reported in heart and kidney transplantations. Most of the information in lung transplant recipients comes from case reports. One retrospective chart

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review performed in the United States showed an incidence of 2.1% and mortality of 40% (4).

In this study, we examined the incidence of Nocardia infection in lung transplant recipients over a course of 17 yr at our institution. The purpose was to provide more information on the epidemiology, risk factors, and outcomes in lung transplant recipients and to complement the data already available.

Methods

We performed a retrospective electronic chart review of our lung transplant recipients from 1990 to 2007. A total of four cases of Nocardia infection in 410 lung transplant recipients were identified. Patient demographics, immunosuppressive regimen at the time of isolation of *Nocardia* sp., previous rejection episodes, use of trimethoprim sulfa (TMP/SMX) for *Pneumocystis carinii* pneumonia prophylaxis, concurrent pathogens, site of infection, radiological findings, and patient outcome were recorded.

Organisms were identified initially in the Clarian microbiology laboratory at Indiana University Medical Center and Methodist Hospital, Indianapolis. The specimens were then sent to the University of Texas Health Science Center, Tyler, Texas, for further testing and subspecies identification.

Nocardiosis was considered a definite diagnosis when *Nocardia* sp. was identified in a clinical specimen of a symptomatic patient. Disseminated infection was defined as Nocardia infection in two or more non-contiguous sites and nocardemia when *Nocardia* sp. can be isolated from blood cultures. Effective antimicrobial treatment was defined as when patients were cured and their clinical signs and symptoms of nocardiosis improved, including microbiological and radiological findings. Death was considered to be secondary to Nocardia infection if the event occurred while they were on treatment for Nocardia. Our local Institutional Review Board approved the study.

Results

Epidemiology

During the 17-yr study period, Nocardia was isolated from 0.97% (four of 410) of our lung transplant recipients. The electronic medical records of these four patients were reviewed. Patient's demographics, *Nocardia* sp., concurrent pathogens at the time of Nocardia isolation, previous rejection episodes, immunosuppressive therapy, Pneumocystis prophylaxis, site of involvement, and antimicrobial therapy were recorded. This information is shown in Tables 1 and 2.

The primary diagnosis leading to lung transplantation was emphysema in three patients and rheumatoid lung disease with pulmonary fibrosis in one patient. The median time to onset with Nocardia infection was 315 d post-transplant. In one patient, the infection occurred within six months of transplantation. In the other three patients, the onset of infection was more than six months. Two of the patients had prior rejection episodes in the preceding six months. All four patients were on Pneumocystis prophylaxis. Three patients utilized TMP/SMX 160/800 mg three times a week. One patient received pentamidine inhalation every month because of sulfa allergy and an episode of methemoglobinemia secondary to dapsone.

Microbiology

Nocardia sp. included *Nocardia nova* in two patients, *Nocardia farcinica* in one and Unspecified *Nocardia* sp. in one patient. Concomitant infection with other organisms was

noted in three patients (Table 2). All of the Nocardia isolates were susceptible to TMP/SMX.

Clinical and radiological characteristics

Nocardia presented as pulmonary infections in all patients, and was identified in bronchoalveolar lavage in three patients and from sputum cultures in the remaining patient. None of the patients had cutaneous or subcutaneous disease and none of them had disseminated infection. There were no distinctive alterations in hematologic or chemical studies in any infected patient.

Chest radiographic findings at the time of isolation of *Nocardia* sp. varied. One patient had no findings on chest radiograph. One patient had a soft tissue density mass in the inferior aspect of left upper lobe. One had a moderate sized area of consolidation in the superior segment of right upper lobe and one had cavitary pneumonia in left upper lobe with reactive pleural effusion.

Treatment and outcome

All of the isolates were susceptible to trimethoprim–sulfamethoxazole, which was utilized to treat all patients. The dosage used was TMP/SMX 160/800 mg p.o. twice daily. One patient was given additional therapy with meropenem for one wk. The duration of therapy varied with clinical and microbiological response of the patient and varied from as short as two months to up to nine months. The only complication related to therapy was a TMP/SMX-induced reduction in red blood cell counts in one patient that recovered when the dose was lowered. None of our patients died from Nocardia infection.

Discussion

Nocardia is a soil borne, aerobic actinomycete that predominately causes disease in patients with deficient cell-mediated immunity (5). In a review of 1050 Nocardia cases, 64% of patients had an associated immune dysfunction (2). To date most of the information about Nocardia infections in transplant recipients came from kidney, heart and heart–lung transplants (1). The incidence in lung transplant recipients has not been well documented and so far there have been only a few published case series, documenting an incidence ranging from 1.85% to 2.1% (4, 6). The incidence at our institute was found to be approximately 1% (four of 410 patients).

The reports have shown that lungs have been involved in the majority of cases with nocardiosis (7). The lungs were the primary sites of infection in all four patients at our institute. No distinct radiological pattern has been identified. Nodules that in some studies have been considered a hallmark of nocardiosis were present in only one patient. The presence of concurrent pathogens also made it difficult to identify whether the finding is due to Nocardia or the other pathogen.

Nocardia appears to have a special tropism for CNS tissue and CNS involvement may be present in up to 20% of patients (8, 9). This is in contradistinction to what we observed. None of our patients had cerebral involvement, which could be explained by absence of disseminated disease.

Cutaneous involvement secondary to hematogenous dissemination is among the most common extra-pulmonary sites of infection mentioned in literature. They are noted to be present in 20% of renal transplant recipients (9). Cutaneous lesions were not observed in any of our patients and this is similar to the other study performed by Husain et al. (4).

Co-infection with other pathogens can occur as the immunosuppressive regimen predispose to other opportunistic organisms (6, 10). Three patients in our report had concurrent infections with other organisms. Two patients had a prior rejection episode in last six months, which may have necessitated an increase in the degree of immunosuppression, leading to increased susceptibility to infection.

The role of trimethoprim–sulfamethoxazole prophylaxis for *Pneumocystis jiroveci* pneumonia in preventing Nocardia infection has been unclear. It has been proposed that trimethoprim–sulfamethoxazole prophylaxis is efficacious in heart transplant recipients (11), but it has not been consistently shown over multiple studies. Similarly in renal transplant patients, the benefits of trimethoprim–sulfamethoxazole as *Pneumocystis jiroveci* pneumonia prophylaxis on Nocardia prevention has not been well documented. There are some data that HIV-infected individuals may have a decreased incidence of having Nocardia infections if they are on Pneumocystis prophylaxis (9). All of our patients were on Pneumocystis prophylaxis when they developed Nocardia infection. This is similar to the study by Husain et al. (4), which showed that 60% of their patients were on trimethoprim–sulfamethoxazole prophylaxis. At this point, it would be difficult to extrapolate from existing data that trimethoprim–sulfamethoxazole in doses for Pneumocystis prophylaxis will prevent Nocardia infection.

Trimethoprim–sulfamethoxazole remains the mainstay of therapy at current time for treatment of Nocardia infections (11, 12). Unfortunately, an optimal treatment protocol has not been well defined in immunosuppressed patients. The use of trimethoprim–sulfamethoxazole has been associated with a high frequency of adverse events and therefore other agents have been increasingly used for Nocardia treatment. They include imipenem, amikacin, third generation cephalosporins, minocycline, moxifloxacin, linezolid, and dapsone (13). There are currently no clinical trials comparing the various agents and it would be extremely difficult to design a good prospective clinical trial because of the low incidence of Nocardia infections. It has also been suggested that in patients who are on trimethoprim–sulfamethoxazole for prophylaxis, other agents should be initiated for treatment but at this time there is no consensus on that approach. Because of the adverse effect profile of trimethoprim–sulfamethoxazole, some experts are of the opinion that either imipenem monotherapy or imipenem in combination with amikacin should be started as first line therapy. As shown recently, linezolid might be a second line option with its good bioavailability and ease of administration. All our patients were treated with trimethoprim–sulfamethoxazole, with one of them requiring one wk of meropenem in addition. The dose of trimethoprim–sulfamethoxazole was reduced in one patient because of decreased blood cell counts.

The optimal duration of therapy is not known. A prolonged course of therapy has been recommended because of the relapsing nature of the infection. All immunocompromised patients regardless of the site of infection and patients with CNS disease should be treated for at least one yr (14). The duration of therapy in our study varies from two to nine months. A recurrence was observed in one patient who was treated for two months.

The mortality rate associated with Nocardia infection ranges from 26% to 63% depending on co-morbidities, degree of immunosuppression, HIV status, presence or absence of cancer, and disseminated disease. The mortality rate in lung transplant recipients was 75% in the study by Husain et al. (4), and 70% in heart–lung transplant recipients at Alfred Hospital in Melbourne, Australia (6). None of the patients in our study died. The discrepancy in our mortality rates compared with other studies performed on lung transplant recipients with Nocardia infections is unclear. The immunosuppressive regimen used at our institute was

similar to other transplant institutes, so the degree of immunosuppression was the same. Other factors could be the absence of CNS involvement and disseminated disease.

The limitation of our case series is the small number of patients compared with other reports on Nocardia infection in lung transplant recipients, but our study strength lies in the fact that we reviewed the database for a longer duration. The other studies on the same topic involved a database of nine yr in one (4) and 11 yr in the other (6). We reviewed the electronic medical records from 1990 to 2007 for a total of 17 yr and identified four patients.

In conclusion, nocardiosis is an uncommon but important cause of morbidity and mortality in immunocompromised patients. The ability of Nocardia to mimic other infections results in a delay in promptly diagnosing these organisms and this contributes to the increased mortality seen in many reports. Newer diagnostic tools may provide a solution to this problem. Trimethoprim–sulfamethoxazole in doses employed for Pneumocystis prophylaxis does not appear to be enough for preventing Nocardia infections. Although the mainstay of therapy still is trimethoprim–sulfamethoxazole, the high incidence of adverse reactions makes other options including imipenem and linezolid more desirable. Further experience, larger patient series and randomized clinical trials are required to aid in diagnosing and managing these patients and to answer the unanswered questions at present.

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Table 1

Demographic characteristics of lung transplant recipients infected with Nocardia

Demographic characteristic	
Age at diagnosis in yr (median/range)	60 (55–64)
Gender (female/male)	3/1
Ethnicity	
White	4
Time to onset of infection post tx in days (median/range)	315 (133–544)
Weight kg (median/range)	62.08 (45.8–96.3)
Hemoglobin g/dL (median/range)	9.375 (8.3–10.4)
Albumin g/dL (median/ range)	2.63 (1.8–3.4)
Blood group A−/A+/B+	2/1/1
Transplant single/double	4/0
Pneumocystis prophylaxis	4/4
TMP-SMX/dapsone	3/1
Prior episode of rejection in six months	2/4

tx, transplant; TMP-SMX, trimethoprim sulfa.

Table 2

Nocardia isolates, specimen source, site of involvement, concurrent pathogens, radiological findings, and immunosuppression in lung transplant recipients

Patient	Nocardia isolate	Specimen	Site involved	Radiological findings	Concurrent pathogens	Immunosuppression
1	*Nocardia nova*	BAL	Lung	No active disease	MAC	Azathioprine, etanercept, prednisone
2	*Nocardia farcinica*	Sputum	Lung	Cavitary pneumonia of the left upper lobe, pleural effusion, scattered nodules	*Klebsiella pneumonia, Aspergillus fumigatus, Candida glabrata*	Azathioprine, tacrolimus, prednisone
3	*Nocardia* sp.	BAL	Lung	Soft tissue density in left upper lobe	None	Mycophenolate, tacrolimus, prednisone
4	*Nocardia nova*	BAL	Lung	Consolidation in right lower lobe	*Pseudomonas aeruginosa*	Tacrolimus, prednisone

BAL, bronchoalveolar lavage; MAC, mycobacterium avium complex.