Actinomyces and Nocardia Infections in Immunocompromised and Nonimmunocompromised Patients

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A retrospective survey of nocardia and actinomyces infections in five local hospitals was conducted over a 3-year period in El Paso, Texas, a border city, in the southwestern United States. The medical records of 42 patients with suspected nocardiosis or actinomycosis were reviewed. One patient was diagnosed with actinomyces and 12 patients with nocardia. Microbiological data included morphologic characteristics, biochemical profile, and susceptibility testing. Predisposing factors included leukemia, renal insufficiency, renal transplant, and lymphoma. No predisposing factors were found in 67% (n=8) of patients (including the patient with actinomycosis). Twenty-three percent (n=3) of patients had disseminated disease without evidence of underlying disease or immunosuppression. The mortality and morbidity of these infections appeared to be low. (*J Natl Med Assoc.* 1999;91:35-39.)

Key words: actinomyces ◆ nocardia ◆ infection

Actinomycetes is the collective name for eight different families of bacteria that grow as branched, long or short filaments of cells. They are widely distributed in nature and are found in soil, water, and decaying vegetation.[1-3] Of the many different genera classified in the order Actinomycetales, only a few produce disease. Nocardia and actinomyces have been cited as responsible pathogens for opportunistic infections in patients with compromised immune systems such as neoplastic diseases, patients on immunosuppressive therapy, and those with autoimmune disorders.[4-7] However, several recent reports indicate that nocardia and actinomyces can produce infections in patients with no preexisting illness, trauma, or immunosuppressive therapy.[1,4,8]

A retrospective study was conducted over a 3-year period to review and evaluate the clinical features, microbiological findings, and outcomes of patients diagnosed with actinomyces and nocardia infection in El Paso, Texas, a US border town. Twelve cases of nocardiosis were found. Fifty-eight percent (n=7) of the patients were immunocompetent and 42% (n=5) were immunocompromised. Fifty-eight percent (n=7) of the patients had disseminated disease, and seven patients presented with underlying disease. Most patients received sulfonamide therapy or a combination of antimicrobial therapy (a sulfonamide and aminoglycoside or a sulfonamide and third-generation cephalosporin). Antimicrobial combination therapy showed good results in patients with disseminated infection and in severely ill patients. One patient, who presented with involvement of the lungs and the aortic valve, was diagnosed with actinomycosis.

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MATERIALS AND METHODS

Medical and Epidemiologic Data

The records of 42 patients with suspected nocardiosis or actinomycosis were reviewed. One patient was diagnosed as having actinomycosis and 12 patients had nocardiosis. Data, collected from five

local hospitals between October 1994 and November 1997, recorded age, sex, underlying condition, antimicrobial, steroid, and cytotoxic chemotherapy, duration of symptoms before admission, complications, and outcome.

Microbiological Methods

Microbiological identification was done by isolation of the causative organism and microscopic observation of gram-positive filamentous and partially acid-fast bacilli from clinical specimens. Microbiological data included morphological characteristics, biochemical profile, and susceptibility testing. Bronchoscopy, lung biopsies, skin lesions, brain abscess, and blood culture specimens were examined directly by Gram stain and Kinyoun acid-fast stain. Organisms were subcultured on Sabouraud's dextrose agar and blood agar and sent to the local county microbiology laboratory and to BRL Reference Laboratories (San Antonio, Texas) for further identification.

Identification and Analysis of Nocardia Isolates

Nocardia identification was based on a battery of biochemical tests, including hydrolysis of casein, xanthine, hypoxanthine, tyrosine, urea, gelatin, and starch. Isolates also were tested for acid production from lactose, xylose, arabinose, and cellobiose, and susceptibility to lysozyme. Antimicrobial susceptibility was performed with several antibiotics including: tetracycline, minocycline, ampicillin, erythromycin, trimethoprim-sulfamethoxazole, and rifampin by disk diffusion methods. Susceptibility testing was performed only upon physician request.

Identification and Analysis of Actinomyces

Identification of actinomyces was based on the following key characteristics: relation to oxygen, microscopic appearance, rapidity of growth, and biochemical profile. The following biochemical tests were performed: catalase, nitrate reduction, ability to liquify gelatin, acid production from rhamnose, mannitol, trehalose, xylose, and glycerol. In addition, a rapid identification system containing 18 different tests from Innovative Diagnostic Systems (Norcross, Georgia) was performed.

RESULTS

Nocardiosis

Twelve cases of nocardiosis occurred between October 1994 and November 1997 (Table 1). Sixty-seven percent (n=8) of the patients were males (sex ratio was 1.5:1). The patients' ages ranged from 33 to 81 years. Fifty percent (n=6) of the patients were Hispanic (Mexican descendant). Most of these patients were from the El Paso area with two patients having originated from Mexico.

Forty-two percent (n=5) of the patients were immunocompromised. Underlying diseases included renal transplant, cancer, and end-stage renal disease. Fifty-eight percent (n=7) of the patients were immunocompetent, with no preexisting illness or immunosuppressive therapy prior to developing the illness.

The duration of symptoms before admission ranged from 4 weeks to 4 months, with an overall average of 2 months. Clinical manifestations included fever, cough, headache, and weight loss in almost all patients. Four immunocompetent patients developed severe nocardia infections, including two who developed disseminated disease that involved the lungs, skin, and brain, and one patient who presented with a brain abscess. Other sites of involvement included skin lesions in four patients, blood in two patients, and lung involvement in four patients. Two patients died; both had underlying and immunocompromised states.

Most of the patients received sulfonamide therapy; however, a combination therapy of sulfamethoxazole-trimethoprim, third-generation cephalosporin, and another drug such as amikacin was used in four of the severely ill patients with disseminated disease. The duration of treatment in all patients ranged from 2 weeks to 9 months, with an average of 6 weeks.

Actinomycosis

Only one patient was diagnosed with actinomycosis. This patient had a 1.5-year history of fever of undetermined origin with involvement of the lungs and the aortic valve. This patient was treated with penicillin for 9 months with no evidence of relapse.

Microbiological Findings

Nocardia. Microbiological diagnosis was made in all patients by isolation of *Nocardia* species. Positive respiratory specimens included sputum (n=1), bronchial washings (n=3), and lung biopsy (n=1). Four specimens from skin lesions (forearm, leg, hip, and chest abscess) and skin biopsies yielded positive culture for *Nocardia* species. Two blood cultures and one specimen from brain tissue yielded gram-posi-

Table 1. Clinical Features, Complications, and Outcomes of Nocardia and Actinomyces Infections

Patient/ Age/Sex	Underlying Disease	Duration of Symptoms	Isolate	Complications	Treatment	Outcome
1/81/M	None	4 months	*Nocardia asteroides*	Disseminated	Ceftriaxone, amikacin, TM-STX	Alive
2/69/M	Crohn's	6 weeks	*Nocardia asteroides*	Brain abscess, disseminated	Ceftriaxone, amikacin, TM-STX	Alive
3/56/F	Renal transplant	2 weeks	*Nocardia* sp	Disseminated	TM-STX	Alive
4/71/F	Lymphoma	6 weeks	*Nocardia* sp	Respiratory failure, disseminated	TM-STX, ceftriaxone	Deceased
5/65/M	Renal transplant diabetes	4 weeks	*Nocardia* sp	Skin abscess, disseminated	TM-STX, ceftriaxone	Deceased
6/33/F	Nephropathy transplant	4 weeks	*Nocardia asteroides*	Disseminated	Ceftriaxone, amikacin	Alive
7/62/M	None	3 weeks	*Nocardia asteroides*	Pulmonary empyema, disseminated	TM-STX	Alive
8/68/F	None	4 months	*Nocardia asteroides*	None	TM-STX	Alive
9/72/M	Diabetes	3 months	*Nocardia asteroides*	None	TM-STX	Alive
10/54/M	None	3 weeks	*Nocardia* sp	None	TM-STX, metronidazole	Alive
11/63/M	None	4 weeks	*Nocardia asteroides*	None	TM-STX, imipenem	Alive
12/65/M	Renal failure	4 months	*Nocardia asteroides*	None	Ceftriaxone	Alive
13/48/M	None	1.5 years	*Actinomyces meyeri*	Endocarditis, disseminated	Penicillin	Alive

TM-STX=trimethoprim-sulfamethoxazole.

tive branching bacilli. *Nocardia asteroides* was recovered from eight patients. Identification at the species level was not possible for four isolates. In all cases, identification was based on the failure to hydrolyze casein, xanthine, hypoxanthine, and tyrosine and the ability to hydrolyze urea and grow in the presence of lysozyme.

Actinomyces. Three sets of blood cultures yielded a gram-positive filamentous, nonspore-forming bacilli. The organism grew slowly in the Bactec anaerobic bottle NR7 and it failed to grow in the presence of oxygen. Cultures were sent to BRL Reference Laboratories for final identification. A battery of biochemical tests gave the following results: failure to produce catalase and nitrate reductase, and inability to liquify gelatin. The organism produced acid from glycerol and xylose but failed to ferment trehalose, mannose, and rhamnose. In addition, a rapid panel containing 18 biochemical tests was inoculated with the isolate. A computer-generated code identified the isolate as *Actinomyces meyeri.*

Case Reports

The clinical features, evolution, and prognosis of three selected cases are described below.

Case 1: Disseminated Nocardiosis Without Underlying Immunosuppression. An 81-year-old Hispanic man presented with fever, weight loss,

cough productive of greenish sputum, and multiple skin masses over the abdomen, lower extremities, and back. The physical examination was remarkable for a temperature of 101.1°F and bilateral crackles on chest examination. He had multiple raised lesions that were nonerythematous and nontender over the back, lower extremities, and abdomen. The laboratory studies were unremarkable. The chest radiograph showed evidence of multiple nodular lesions in both lung fields. Bronchoscopy and biopsy of the lung showed evidence of multiple branching gram-positive elements. Biopsy of one of the skin lesions revealed the same pathogenic morphology. Cultures grew *N asteroides.*

The patient had no evidence of underlying immunosuppression and was treated with ceftriaxone, amikacin, and sulfamethoxazole-trimethoprim for 6 weeks followed by 7 months of sulfamethoxazole-trimethoprim alone. No evidence of relapse was noted after 1 year of follow-up.

Case 2: Disseminated* N asteroides *in a Relatively Immunosuppressed Host. A 69-year-old man was admitted with a 3-month history of persistent cough, weight loss, and mental status changes. His history was significant for Crohn's disease for which he was placed on prednisone. He was previously treated unsuccessfully with several antibiotics.

On admission, he had a temperature of 100.4°F and was slightly confused. Three skin lesions were noted over his lower extremities, back, and abdomen. The chest radiograph showed a right lower infiltrate. Magnetic resonance imaging of the head revealed several scattered brain abscesses. Laboratory studies were unremarkable. Bronchoscopy and biopsy of the lung eventually grew *N asteroides.* Biopsy of the skin lesions grew the same pathogen.

The patient responded clinically to 6 weeks of sulfamethoxazole-trimethoprim, ceftriaxone, and amikacin followed by 8 months of sulfamethoxazole-trimethoprim with no evidence of relapse.

Case 3: Disseminated* A meyeri *Infection in a Nonimmunocompromised Host. A 48-year-old man presented with a 1.5-year history of intermittent high-grade fevers, cough, and weight loss. He had been evaluated by several physicians in several centers for the same problem without a diagnosis. Previous chest radiographs showed bilateral interstitial changes, and biopsy of the lung, including an open-lung biopsy, was unremarkable.

On admission, he had a temperature of 103°F and was cachexic and malnourished. A complete blood cell count and other routine laboratory studies were unremarkable. Three sets of blood cultures grew *A meyeri.* An echocardiogram confirmed the presence of a large vegetation on the aortic valve.

The patient was placed on penicillin and responded dramatically with rapid clearing of the bacteremia and pulmonary infiltrates, and resolution of the vegetation as evidenced by repeat transesophageal echocardiograms. He was treated for 9 months and had no evidence of relapse after 6 months of follow-up.

DISCUSSION

Nocardia and actinomyces are filamentous, branching, gram-positive bacilli that belong to the family Actinomycetaceae.[1,3,9] These ubiquitous soil-borne saprophytic organisms are capable of causing localized or disseminated infections. Nocardia infection is commonly introduced through the respiratory tract by inhalation of airborne conidia from soil or other environmental sources.[1,8,10] The lung is the most commonly affected primary site of the initial infection.[10,11] Cutaneous involvement may result from primary inoculation through the skin or hematogenous dissemination.[10] Systemic nocardiosis is rare, but when it is present, disseminated infections occur more often in immunocompromised patients.[5,11]

Unlike nocardiosis, actinomycosis is an endogenous disease. Etiologic agents are part of the normal flora of mucous membranes such as the oral cavity. Infection and disease often are associated with trauma, surgery, or aspiration pneumonia. Once actinomycosis is established locally, dissemination usually occurs by the hematogenous route. Like nocardiosis, disseminated infection due to actinomycetes is thought to occur most often in debilitated patients or in patients with impaired immune systems such as those with autoimmune disorders, malignancy, acquired immunodeficiency syndrome (AIDS), and immunosuppressive therapy.[4,9,10,12] However, some reports indicate that nocardia, as well as actinomyces, are capable of causing infection in patients with no identifiable predisposing factors or evidence of immunosupression.[1,11,13]

In the present study, 12 cases of nocardiosis were diagnosed. Eight of these cases were in men who had symptoms consistent with previous observations of a male preponderance for nocardiosis.[10,14] Seven patients presented with disseminated disease,

two of whom did not have evidence of underlying disease or immunosuppression. Underlying disease was found in 6 of 12 patients: lymphoma (n=1), end-stage renal disease (n=2), and renal transplant (n=3). Two patients died. These patients presented with disseminated infection and were immunosuppressed. In contrast to some reports in the literature, no difficulty in diagnosis was noted, and the mortality rate in disseminated infection appears to be low (28%).

A high number of immunocompetent patients developed nocardiosis 58% (7 of 12 patients). This percentage is higher compared with the 10% to 40% reported in most studies in the literature.[1,10,15] However, most recent studies have reported similar figures (50% to 57%).[11] The reason for this increased incidence is unknown but could be due to a more aggressive diagnosis, raised suspicion, or better medical technology.

Presumptive nosocomial nocardiosis has been reported only in immunocompromised patients,[6,16] and exposure to dust and soil appears to be a risk factor for acquiring these infections. Therefore, considering the climate and arid conditions of the Southwest, it could be possible that these conditions may contribute to the high incidence observed in this study.

Nocardia asteroides was the most common isolate. However, full identification was not obtained for four isolates. Isolation and identification of *Nocardia* species is not an easy task. These organisms are slow growers and require prolonged incubation periods. Cultures should be maintained for at least 3 weeks before ruling out any positive results. Media for testing biochemical reactions are observed at 2-day intervals for a period of 2 weeks or until good growth occurs.

CONCLUSION

Although effective antimicrobial therapy against nocardia infection is available, an optimal antimicrobial protocol has not been established especially in immunocompromised patients. Factors affecting implementation of an optimal antimicrobial therapy regimen include lack of standardization in susceptibility testing (mainly due to the difficulty in interpreting results) and poor correlation between in vitro testing and in vivo clinical efficacy.[1,15,17] Sulfonamides remain the mainstay of therapy when these organisms are suspected. Combined antimicrobial therapy has been reported to work well, and synergistic effects have been observed with drugs such as imipenem and amikacin as well as amikacin and cefotaxime.[4,10,15] The optimal duration of antimicrobial therapy is unknown. A prolonged course of therapy is indicated due to the chronic nature of nocardia and the possibility of relapse.

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