Clinical experiences of pulmonary and bloodstream nocardiosis in two tertiary care hospitals in northern Taiwan, 2000-2004

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Background and Purpose: *Nocardia* is an uncommon pathogen in humans, and most patients with nocardiosis are immunocompromised, with variable etiologies. To understand the incidence, clinical characteristics, treatment and outcome of pulmonary and bloodstream nocardiosis, we conducted a retrospective study in two tertiary care hospitals in northern Taiwan.

Methods: We reviewed laboratory culture reports and clinical records of 29 adult patients with lower respiratory tract or bloodstream nocardiosis (21 and 8 patients, respectively) in two tertiary care hospitals, over a period of 5 years. The risk factors, clinical manifestations, response to therapy, outcome and recurrence rate were compared between these two groups.

Results: The most common underlying conditions in pulmonary nocardiosis were chronic lung disease and long-term steroid usage. For nocardemia, underlying malignancy and steroid administration are common. Fourteen of 21 patients with pulmonary nocardiosis ever transferred to an intensive care unit and 9 of them had concomitant infection. In patients with and without coexisting isolates during hospital course, the mean days from admission to specific therapy for nocardiosis were 26.4 and 11.9 days, respectively. Patients with nocardemia showed great variation in clinical manifestations and disease severity; central venous catheter implantation was noted in 6 of them. Only one patient with nocardemia had documented recurrence. Twenty four patients were treated with antimicrobials (trimethoprim-sulfamethoxazole, 83%; imipenem or meropenem, 25%). Treatment failure occurred in 7 of 20 patients treated with trimethoprim-sulfamethoxazole alone or in combination.

Conclusions: Pulmonary or disseminated nocardiosis is rare but may be fatal as an opportunistic infection in an immunocompromised host with chronic lung disease, underlying malignancy or long-term steroid usage. The significance of primary nocardemia needs careful evaluation. Concomitant infection was the probable predisposing factor for intensive care unit admission for pulmonary nocardiosis in our study (*p*=0.019) and might obscure the isolation of nocardiae organisms and delay effective treatment. For critical patients with nocardiae infection, initial therapy with a combination antimicrobial regimen is recommended.

Key words: Bacteremia; Lung diseases; *Nocardia* infections; Opportunistic infections; Risk factors

Introduction

Nocardia spp., belonging to the genus of aerobic actinomycetes, are environmental saprophytes, living in soils, water and organic matter. They are Gram-positive and weakly acid-fast, branching bacteria whose hyphae are often fragmented to coccobacillary forms [1]. *Nocardia* spp. are facultative intracellular pathogens, and the pathogenesis of nocardiosis is complicated. The major virulent factors are resistance to phagocytosis by filamentous log-phase cells, inhibition of phagosome-lysosome fusion, and the complex cell wall glycolipids.

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Host resistance to nocardiae infection depends on neutrophils in early lesions and then the cell-mediated immune response [2]. The most common predisposing factors of opportunistic nocardia infection are chronic obstructive pulmonary disease, neoplastic disease, long-term steroid usage, and human immunodeficiency virus infection [3,4]

Clinical manifestations of nocardiosis range from cutaneous infections caused by traumatic inoculation in normal hosts to severe pulmonary and central nervous system diseases in immunocompromised hosts. Although this pathogen is ubiquitous in the environment, the literature review of nocardiosis is limited, especially bloodstream infections [5]. To understand the incidence, clinical manifestations, response to therapy and outcome of nocardiosis, we conducted a retrospective study of the patients with pulmonary nocardiosis and nocardemia in two medical centers over a period of 5 years.

Methods

The study enrolled patients older than 18 years who were hospitalized with pulmonary or bloodstream infection with *Nocardia* spp. during the period of study in two tertiary care hospitals. The period of review was between January 2000 and February 2005. A diagnosis of pulmonary nocardiosis required at least one positive culture from respiratory samples, and the presence of clinical symptoms and a new lesion on chest film at admission. The respiratory samples included expectorated sputum, endotracheal aspiration, pleural effusion, bronchioalveolar lavage or lung tissue obtained from biopsy. Patients who had at least one set of positive blood cultures were defined as nocardemia. If a patient had multiple episodes of nocardiosis during the study period, the first episode only was included. One patient with bacterial growth in both sputum and blood was categorized in the pulmonary group, as the lung was the probable primary site. This case has been reported in the literature and was also enrolled in this study [6].

Long-term steroid usage was defined as prescription of oral prednisolone at least 10 mg/day for more than two months before the infection episode. The diagnoses of underlying diseases were made according to medical records. Patients who had any one of bronchiectasis, chronic obstructive pulmonary disease or pneumoconiosis with previous symptoms and compatible old lesions on chest films were categorized as

underlying chronic lung disease. Chest X-ray films were reviewed, and the new lesions were the identified findings compared with available previous films. The clinical manifestations were the chief complaints while admitted to hospital.

The identification of *Nocardia* spp. was based on the appearance of predominant colonies on common media for aerobic bacteria (including blood agar, eosin methylene blue, and chocolate agar). Microbiological diagnosis was made if the subculture colony revealed a unique morphology as Gram-positive branching, beaded, filamentous bacteria [2]. Species identification was not done in almost all cases in the two hospitals. Antimicrobials which had been administered for more than 3 days were included in the analysis. Concomitant infection during this episode was defined as other coexisting microorganisms isolated within 2 weeks before or after the day of intensive care unit (ICU) admission or within two weeks before death. The duration of effective antibiotic administration included both parenteral and oral drugs prescribed on an outpatient basis. Mortality was defined as death from all causes during the study episode of hospitalization. Recurrence data was obtained for clinical follow-up for at least one year after the patient was discharged. We chose the Student's *t* test as the statistical technique for data analysis.

Results

During this study period, 21 patients with pulmonary nocardiosis and eight with nocardemia were recruited. Demographic and clinical data are listed in Table 1. The male-to-female ratio was 2.5 in the pulmonary group and 1.67 in the nocardemia group. The mean age was 68 years in the pulmonary group and 69.4 years in the nocardemia group. Both the ICU admission rate (66.7% vs 11.1%, p=0.009) and mortality rate (42.8% vs 11.1%, p=0.009) were significantly higher in the pulmonary group compared with the nocardemia group.

Four patients had 2 different underlying chronic illnesses, and the other 25 patients had at least one. Anti-human immunodeficiency virus antibody was checked in 6 patients, and all were negative. The most significant risk factor in both groups was long-term steroid usage. In the pulmonary group, chronic lung disease was a common predisposing factor. In the nocardemia group, underlying malignancy was a significant risk factor *(p<0.05)*, although the sample size is small. Clinical manifestations were nonspecific in

Table 1. Clinical characteristics of patients with pulmonary and bloodstream nocardiosis

Characteristic	Pulmonary nocardiosis (n = 21) No (%)	Nocardemia (n = 8) No (%)	p
Age (years; mean)	68.0	69.4	
Male gender	15 (71.4)	5 (62.5)	0.642
ICU admission	14 (66.7)	1 (11.1)	0.009
Mortality	9 (42.8)	1 (11.1)	0.009
Average hospital stay (days) [range]	53.7 (5-336)	25 (7-56)	0.226
Average antibiotic treatment (days) [range]	37.6 (5-168)	31.5 (14-42)	0.08
Clinical manifestation			
Fever	10 (47.6)	2 (25)	0.269
Dyspnea	9 (42.6)	3 (37.5)	0.793
Cough	9 (42.6)	2 (25)	0.375
General malaise	1 (4.7)	2 (25)	0.11
Chest pain	3 (14.2)	0 (0.0)	0.258
Others	2 (9.5)[b]	1 (12.5)[c]	
Underlying illness			
Steroid therapy	10 (47.6)	3 (37.5)	0.624
Chronic lung disease			
COPD	8 (38)	1 (12.5)	0.182
Pneumoconiosis	2 (9.5)	1 (12.5)	0.814
Bronchiectasis	1 (4.3)	0 (0.0)	0.529
Diabetes mellitus	2 (9.5)	1 (12.5)	0.814
Organ transplantation	1 (4.8)	0 (0.0)	0.529
Chronic hepatitis	1 (4.8)	1 (12.5)	0.462
Ischemic heart disease	1 (4.8)	0 (0.0)	0.529
Malignancy (total no.)	0 (0.0)	4 (50)	<0.001
None documented[a]	4 (19.0)	1 (12.5)	

Abbreviations: ICU = intensive care unit; COPD = chronic obstructive pulmonary disease
[a]No documented or known underlying illness at admission.
[b]Sore throat, arthralgia.
[c]Dead on arrival.

both groups, but acute symptoms during this episode (e.g., fever, dyspnea and cough) were more common in the pulmonary group.

The microbiological results and clinical relationships in patients with pulmonary nocardiosis are listed in Table 2. Eleven of 21 patients had coexisting isolates during hospitalization, and 9 of them received specific therapy for nocardiosis. The mean time from admission to specific therapy was 26.4 days. Of the 10 patients without coexisting isolates, 8 received antimicrobials and the mean time from admission to specific therapy was 11.9 days. Concomitant infections were noted in 9 of 14 patients who were transferred to ICU due to respiratory distress. Only 1 of 7 patients without ICU admission had concomitant infection.

The characteristics of patients with nocardemia are listed in Table 3. Six of 8 patients had a central venous catheter implantation before blood sample collection. Five patients had new lesions on chest films. Pulmonary infection might have been the origin of nocardemia in 3 of them according to image findings and clinical manifestations (cases 2, 4, and 5). Case 6 was diagnosed as endocarditis with mitral valve vegetation but no other pathogen was isolated. In four patients, the primary source of nocardemia was indeterminate.

Five of 29 patients did not receive antibiotic therapy. Of them, four had nocardemia, and two died. The fatal case (case 9, Table 2) with pulmonary nocardiosis was not enrolled for antibiotic analysis because of short-term hospital stay (<2 days). Case 7 with nocardemia did not receive antimicrobial therapy before death. Case 1 with nocardemia had no symptoms of active infection during his episode. However, recurrence with fever was documented 2 months later. Cases 3 and 8 with nocardemia resolved without specific therapy.

Among the 24 patients who received antibiotic therapy, 8 patients (33.3%) died and all had pulmonary nocardiosis. The commonly prescribed antibiotics were: trimethoprim-sulfamethoxazole (83.3%) and carbapenems (imipenem or meropenem, 25.0%). The

Table 2. Microbiological results and clinical characteristics in patients with pulmonary nocardiosis

Case no.	Concomitant infection (source)	Duration from admission to specific therapy (days)	Specific therapy (duration [days])	ICU stay	Concomitant infection before or after ICU admission	Duration from last coexisting isolate to fatality (days)	Duration from last nocardiae isolation to fatality (days)	Hospital stay (days)	Outcome
1	–	8	SXT, IPM (21)	Yes	No	–	9	28	F
2	*Mycobacterium intracellulare* (S)	36	SXT, IPM (10)	Yes	No	45	9	42	F
3	(1)[a] *Streptococcus viridans* + *Haemophilus influenzae* + *Prevotella melaninogenica* (BAL) (2) *Pseudomonas aeruginosa* (S)	20	SXT, MEP (3)	Yes	Yes	8	8	23	F
4	–	7	SXT (21)	Yes	No	–	23	28	F
5	*Escherichia coli*-ESBL (BAL)	15	SXT (4)	Yes	Yes	5	6	21	F
6	(1) *Enterobacter cloacae* (B) (2) *Escherichia coli* (U)	37	SXT (28)	Yes	Yes	46	35	63	F
7	(1) *Acinetobacter baumannii* (S) (2) MRSA (S)	9	SXT (14)	Yes	Yes	18	21	21	F
8	MSSA (W)	–	AM/CL (7)	No	No	5	2	7	F
9	–	–	–	No	No	–	–	14	F
10	–	20	SXT (63)	No	No	–	–	42	C
11	–	5	SXT (245)	Yes	No	–	–	14	C
12	–	5	SXT (28)	No	No	–	–	28	C
13	(1) *Acinetobacter baumannii* (S) (2) *Stenotrophomonas maltophilia* (S)	22	SXT, IPM (28)	Yes	Yes	–	–	63	C
14	(1) *Pseudomonas aeruginosa* (S) (2) *Acinetobacter baumannii* (S)	24	IPM (14)	Yes	Yes	–	–	35	C
15	(1) *Salmonella choleraesuis* (B) (2) *Stenotrophomonas maltophilia* (S) (3) *Acinetobacter baumannii* + MRSA (S)	–	CRO (42)	Yes	Yes	–	–	42	C
16	(1) *Pseudomonas aeruginosa* (S) (2) *Klebsiella pueumoniae*-ESBL (S)	3	SXT (21)	Yes	Yes	–	–	21	C
17	–	7	SXT (42)	No	No	–	–	14	C
18	(1) *Salmonella enteritidis* (SY) (2) *Cryptococcus neoformans* (B) (3) *Acinetobacter baumannii* + *Pseudomonas aeruginosa* (S)	72	SXT (84)	Yes	Yes	–	–	168	C
19	–	–	CXM (5)	No	No	–	–	5	C
20	–	29	SXT (336)	No	No	–	–	35	C
21	–	14	SXT, IPM, AN (56)	Yes	No	–	–	77	C

Abbreviations: ICU = intensive care unit; S = sputum; BAL = bronchioalveolar lavage; ESBL = extended-spectrum beta-lactamase; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-susceptible *Staphylococcus aureus*; B = blood; U = urine; W = wound; SY = synovial fluid; SXT = trimethoprim-sulfamethoxazole; IPM = imipenem; MEP = meropenem; AM/CL = amoxicillin-clavulanate; CRO = ceftriaxone; CXM = cefuroxime; AN = amikacin; F = fatality; C = cure
[a]Numbered in sequence.

dosage of trimethoprim was about 10 to 16 mg/kg/day. Other antibiotics used were cefuroxime (8%), ceftriaxone (8%), and amoxicillin-clavulanate (8%).

Carbapenem and trimethoprim-sulfamethoxazole combination therapy was administered initially in three patients, and two of them resolved. Two of the

Table 3. Clinical characteristics of patients with nocardemia

Case no.	Underlying condition	Symptoms	CVC before culture	New lesions on CXR	Bottle number (positive cultures/total)	Days needed for culture	Treatment (days)	Outcome
1	CML	General weakness and dysuria	Yes	No	2/2	5	–	Cure
2	COPD, Pneumoconiosis	Dyspnea and cough	No	RUL abscess, cavitation	1/2	15	SXT (42)	Cure
3	Rectal cancer	Dyspnea	Yes	Bilateral lung small nodules	1/2	7	–	Cure
4	CRF	Fever	Yes	Alveolar infiltration	1/2	5	SXT (28)	Cure
5	Non-Hodgkin's lymphoma, DM, chronic hepatitis B	Fever and productive cough	Yes	Alveolar infiltration	2/2	3	SXT (42)	Cure
6	Ulcerative colitis	General weakness	No	No	2/2	9	SXT (14)	Unknown[a]
7	Small cell lung cancer and colon cancer	Dyspnea	Yes	No	2/2	4	–	Fatality
8	Not documented	OHCA, VT	Yes	Alveolar infiltration	1/2	13	–	Cure

Abbreviations: CVC = central venous catheter; CXR = chest X-ray; CML = chronic myeloid lymphoma; COPD = chronic obstructive pulmonary disease; CRF = chronic renal failure; DM = diabetes mellitus; OHCA = out-of-hospital cardiac arrest; VT = ventricular tachycardia; RUL = right upper lobe; SXT = trimethoprim-sulfamethoxazole
[a]Patient self-discharged after partial treatment.

patients who died were treated with trimethoprim-sulfamethoxazole to which carbapenem was added later due to poor response. The mean duration of treatment was 53 days in the pulmonary group and 32 days in the nocardemia group. There was a large variation in the duration of treatment (from 7 to 336 days).

In total, 19 patients (12 with pulmonary nocardiosis and 7 with nocardemia) were discharged with stable condition. Only one patient experienced recurrent nocardemia, 2 months later. However, four patients died within one year (2 in the pulmonary group and 2 with previous nocardemia). Seven patients (3 in the pulmonary group and 4 in the nocardemia group) were lost to follow-up within one year. Only 6 patients with pulmonary nocardiosis continued follow-up until April 2007, and no recurrence was noted.

Discussion

The nocardiae are slow-growing organisms and may be difficult to recover and identify routinely in a busy microbiological laboratory. In mixed cultures of clinical specimens, the nocardiae are easily obscured by other rapidly growing bacteria. Delayed growth may lead to the premature disposal of cultures [2]. In this study, the mean time from admission to specific therapy of nocardiosis in patients with and without concomitant

infection was 26.4 and 11.9 days. Without notification, clinicians may also possibly consider the *Nocardia* spp. as contamination or colonization. Dismissing positive cultures as harmless is not favored, especially in critical patients.

In addition to difficulty of culture, the identification of *Nocardia* spp. is labor-intensive and is not performed routinely in service laboratories. Thus, the actual prevalence is probably underestimated in both hospitals. Promising new methods include the 16S polymerase chain reaction-based assay for the rapid detection of *Nocardia* spp. and polymerase chain reaction-restriction fragment length polymorphism using restriction enzymes *Msp*I, *Hin*fI, *Bsa*HI, *Hae*III and *Bst*EII. These methods were all published in 2005, and are believed to be sensitive, specific, and rapid, but need prospective evaluation in larger clinical populations [7-9].

In our review, male gender and older patient age predominanted in the population with nocardiae infection. This trend is compatible with other series of reviews [10]. However, variable clinical manifestations and hospital courses have been noted. As an opportunistic infection, different host immune states may explain the large variations in disease severity of nocardiosis.

Classically, the isolation of *Nocardia* spp. from blood culture has been considered as indicating

disseminated infectious disease. We are aware of only a single patient reported in the literature with disseminated nocardiosis diagnosed by positive culture results from a source other than blood [6]. The reported associated risk factors of nocardemia are underlying malignancy and central venous catheter usage [11-13]. Six of 8 patients in our review had temporary or permanent central venous catheter implantation before blood sample collection.

In a review of positive blood cultures over 4 years, among eight patients with *Nocardia* spp., only one patient had definite evidence of nocardiae disease. Contamination or transient bacteremia was suggested, in view of the favorable outcome [5]. In that study, 7 of 8 cases had only one bottle of positive culture. We found 4 of our 8 patients with nocardemia had 2 bottles of positive culture and the mean time for culture report was 5.2 days. Thus, contamination might be less likely. Two of the patients received trimethoprim-sulfamethoxazole, but nocardemia relapsed 2 months later. The fatal case without therapy was due to short time of stay. The other 4 patients who had only a single bottle of positive culture had new lesions on chest X-ray films, and two of them had active symptoms then treated as pneumonia. At present, the significance of nocardemia is still a clinical judgment, and more cases and detailed laboratory study are essential to make further conclusions.

Our results with regard to age and gender distribution, predisposing factors, clinical manifestations and radiographic findings are similar to previous reviews [3,4,10]. The ICU admission rate and mortality rate were higher in the pulmonary group. Of 14 patients with severe pulmonary nocardiosis transferred to ICU, 9 had concomitant infections. In our study, the concomitant infection is a probable predisposing factor for ICU admission (p=0.019). The in-hospital mortality rate in our study (42.8%) was higher than in some others [10,14]. Six of 10 fatal cases had co-existing isolates. In 3 of them (cases 3, 5, 8; Table 2), the isolates were recovered within 2 weeks before death and the time from last nocardiae isolation to fatality and the treatment duration was also short. In contrast, except in one patient admitted to the ICU following an out-of-hospital cardiac arrest, no concomitant pathogen was isolated in the primary nocardemia group. Thus, concomitant infection might also be a contributory factor in death from nocardiosis.

Optimal antimicrobial regimens have not been established by controlled clinical trial. The duration of treatment has not been well defined, and most authorities recommend that therapy for immunocompetent patients with pulmonary or systemic nocardiosis (excluding central nervous system involvement) should be continued for at least 6 months [15].

Although trimethoprim-sulfamethoxazole is still the main therapy of nocardiosis, mortality with sulfonamide monotherapy may be as high as 50% [15]. *Nocardia farcinica*, the pathogen identified from the blood and respiratory samples of the patient with disseminated nocardiosis, is a potential multidrug-resistant strain [16,17]. For empirical therapy prior to the identification of species and susceptibility results, most experts recommend a three-drug regimen consisting of trimethoprim-sulfamethoxazole, amikacin, and either ceftriaxone or imipenem for patients with serious disease [2]. Because lack of species identification and antimicrobial susceptibility testing are commonplace, the majority of antibiotic selection is by experience and clinical judgment. The situation regarding drug resistance is not clear in our study. Twenty patients had been treated unsuccessfully with trimethoprim-sulfamethoxazole, and mortality resulted in seven of them. Initial combination therapy with trimethoprim-sulfamethoxazole and carbapenem was associated with a better outcome than sequential administration, although the case number is small. Refractory nocardiosis might be the major cause of fatality in 2 of 10 fatal cases (cases 1 and 4; Table 2). In addition to amikacin plus imipenem, monotherapy with linezolid was also effective in in vivo [18] and in vitro studies [19]. For critical patients with nocardiosis and poor response to therapy or drug allergy, linezolid might be an alternative choice before antimicrobial susceptibility test results are available.

In conclusion, nocardiosis is an opportunistic infection with nonspecific or subclinical presentations, and a subacute disease course with large variations. The significance of subclinical primary nocardemia should be carefully evaluated. Concomitant infection is the probable contributory factor of ICU admission for pulmonary noccardiosis and might obscure the recovery of nocardiae isolates and thus delay treatment. For critical patients with risk factors and poorly controlled pulmonary nocardiosis, early combination therapy is recommended.

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