

## Isolation of *Nocardia* Species in Patients With Cystic Fibrosis

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The isolation of *Nocardia* species from the respiratory secretions of patients with cystic fibrosis presents problems with important clinical implications. From the sputum culture of a total of 387 patients with cystic fibrosis, *Nocardia* species was isolated in 9 cases (2%; 8 females and 1 male) with a mean (SD) age of 17 (7) years. Sixty-seven percent of the patients were asymptomatic and no relevant radiographic or analytical changes were detected. In only 3 patients was *Nocardia* species isolated again in successive samples. Two patients were not treated, 7 were treated with cotrimoxazole and 3 with minocycline; in 2 cases therapy was intravenous. After a mean follow-up of 48 (33) months, all patients had improved. Isolation of *Nocardia* species from the secretions of patients with cystic fibrosis does not necessarily imply infection and the need for treatment should be assessed on an individual basis.

**Key words:** *Cystic fibrosis*. *Nocardia species*. *Nocardiosis*.

### Introduction

Cystic fibrosis is a recessive autosomal disease caused by mutations in the gene that codes for the cystic fibrosis transmembrane conductance regulator, a chloride ion channel in epithelial cells.<sup>1</sup> Although multiple systems are involved, airway infection accounts for most morbidity and mortality. While the presence of *Staphylococcus aureus* and *Pseudomonas aeruginosa* is unanimously accepted as pathogenic,<sup>2</sup> the role of other microorganisms is unclear<sup>3</sup> since their presence in sputum can indicate superficial colonization rather than infection. Such is the case of *Nocardia* species. The clinical significance of a positive

### Aislamiento de *Nocardia* en pacientes con fibrosis quística

El aislamiento de *Nocardia* spp. en las secreciones respiratorias de los pacientes con fibrosis quística (FQ) plantea problemas en cuanto a su trascendencia clínica. De un total de 387 pacientes con FQ, se aisló *Nocardia* spp. en el cultivo de esputo en 9 (2%; 8 mujeres y un varón), con una edad media ( $\pm$  desviación estándar) de  $17 \pm 7$  años. El 67% de los casos se encontraba asintomático y en ningún paciente se detectaron cambios radiológicos ni analíticos de interés. En sólo 3 pacientes el aislamiento se repitió en muestras sucesivas. Dos pacientes no fueron tratados y en los restantes se empleó cotrimoxazol (7 casos), minociclina (3 casos) y tratamiento intravenoso (2 casos). Después de un seguimiento de  $48 \pm 33$  meses, todos los pacientes presentaron una evolución clínica favorable. El aislamiento de *Nocardia* spp. en pacientes con FQ no implica necesariamente infección y la necesidad de tratamiento debe valorarse individualmente.

**Palabras clave:** *Fibrosis quística*. *Nocardia*. *Nocardiosis*.

finding for this microorganism in a sputum sample from a patient with cystic fibrosis is uncertain.

Nocardiosis is caused by various species of the genus *Nocardia*, which belongs to the order of *Actinomycetales*. It can cause lung disease, skin disease, or systemic disorders by involving the central nervous system, but it can also colonize the airways asymptotically.<sup>4-6</sup> Although nocardiosis can affect healthy individuals, the risk is greater in patients with depressed cell-mediated immunity, such as occurs in cancer,<sup>7</sup> acquired or congenital immunodeficiency,<sup>8</sup> or human immunodeficiency virus infection.<sup>9,10</sup> It is also seen in patients receiving treatment with corticosteroids or immunodepressants or those who have a history of lung disease, such as bronchiectasis,<sup>11</sup> chronic obstructive pulmonary disease, asthma, pulmonary fibrosis, mycobacterial infection, tuberculosis, chronic granulomatosis, or alveolar proteinosis.

The objective of the present report was to analyze the clinical characteristics and course in patients with respiratory secretions from which *Nocardia* species were isolated.

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Figure. *Nocardia asteroides*

### Clinical Observations

We collected the records of isolations of *Nocardia* species from patients with cystic fibrosis in all the cystic fibrosis units of the Spanish Autonomous Community of Madrid (at Hospital Universitario La Paz, Hospital Ramón y Cajal, Hospital Universitario de la Princesa, Hospital 12 de Octubre, Hospital Gregorio Marañón, and Hospital Niño Jesús) before and including December 2006.

### Clinical Variables

The following variables were evaluated: age, sex, clinical manifestations, analyses, lung function, previous colonization, radiographic findings, underlying treatment, therapeutic approach, and clinical course. Clinical variables recorded were cough, dyspnea, fever, chest pain, headache, weight loss, or cutaneous lesions. Digestive tract disease (pancreatic insufficiency), liver disease, and diabetes were noted. Likewise, information was gathered on other possible risk factors that could favor a finding of *Nocardia* species in sputum. Also recorded were forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV<sub>1</sub>), expressed as percentages of the reference values of the European Respiratory Society.<sup>12</sup>

### Microbiology

The samples processed were either from spontaneous sputum or, in cases where fibroscopy was performed, from bronchial aspirate. Gram staining was consistently used since it can show the presence of partially branching, acid-fast gram positive bacilli indicative of *Nocardia* species. Culturing was carried out conventionally in common media for bacteria (blood-agar and chocolate-agar cultures) and, to control intense growth of other pathogens, in selective media (such as buffered charcoal-yeast extract- $\alpha$  agar and modified Thayer-Martin agar). In some cases molecular biology techniques were used for species identification (Figure).

Isolates were classified as infections if associated with clinical and radiographic manifestations; if no such

manifestations were present isolates were classified as colonization. Isolates were considered sporadic if detected occasionally in 1 or 2 cultures in 6 months, and chronic if detected 3 or more times in 6 months.<sup>13,14</sup>

Of the 387 patients followed in the 6 cystic fibrosis units, *Nocardia* species were isolated in 9 patients (2.3%), 8 females and 1 male, with a mean (SD) age of 17 (7) years. The isolations were *Nocardia* species (3 cases), *Nocardia asteroides* (2), *Nocardia farcinica* (1), *Nocardia asiatica* (1), *Nocardia elegans* (1), and *Nocardia transvalensis* (1).

Six of the 9 patients (67%) with *Nocardia* species isolations had clinical manifestations. In 3 patients exacerbation was more acute owing to fever, cough, dyspnea, chest pain, and/or hemoptysis; the other 3 only presented a slightly exacerbated cough. In the 3 remaining patients, isolation of *Nocardia* species was a chance finding during routine follow-up.

When *Nocardia* species were isolated, all patients had digestive system manifestations and none were diabetic. Associated chronic colonizations coinciding with isolation of *Nocardia* species were 7 *P aeruginosa*, 5 *S aureus*, 3 *Haemophilus influenzae*, 2 *Stenotrophomonas maltophilia*, 1 *Achromobacter xylosoxidans*, 2 *Aspergillus fumigatus*, and 1 *Candida albicans*. Lung function tests of the patients with *Nocardia* species isolation showed a mean (SD) FVC of 72% (20%) and a mean FEV<sub>1</sub> of 78% (20%). There were no relevant radiographic or analytical changes.

Patients' clinical characteristics and course are shown in Table 1. Regarding risk factors at the moment of isolation of *Nocardia* species, 3 patients were diagnosed with allergic bronchopulmonary aspergillosis and were taking oral corticosteroids; 1 patient was on a continuous dosing schedule of oral antibiotics for *S aureus*; 6 patients were being treated with inhaled corticosteroids, and 8 with daily inhaled antibiotics (Table 2).

Six patients were taking cotrimoxazole in doses of 10-15 mg/kg (maximum, 160 mg every 8 hours); 3 patients were taking minocycline in doses of 100 mg every 12 hours; 2 patients, intravenous imipenem-amikacin and meropenem-tobramycin, respectively; and 2 patients, no treatment.

Cultures from 6 patients showed positive results only at the first analysis, whereas in the cultures of the other 3, *Nocardia* species were repeatedly isolated. After a mean (SD) followup of 48 (33) months' clinical evolution, cultures were negative for all patients.

### Discussion

In recent years greater survival as been achieved in patients with cystic fibrosis thanks to the development of a variety of treatment regimens, especially those for the containment of respiratory infection. Although *P aeruginosa* and *S aureus* are the most common pathogens related to morbidity and mortality in cystic fibrosis patients, the significance and incidence of other pathogens are as yet unknown.<sup>3</sup>

The presence of microorganisms in sputum cultures does not always imply disease but rather simple colonization of the airways with no destruction of pulmonary tissue and no signs or symptoms of infection.

TABLE 1  
 Characteristics of Patients With Cystic Fibrosis and Isolation of *Nocardia* Species in Sputum

Case	Sex	Age, y	History of Chronic Colonization	Symptoms	FVC, %	FEV <sub>1</sub> , %	Species, No. of Isolates	Treatment	Follow-Up, mo
1	F	14	<i>Pseudomonas aeruginosa</i> , <i>Staphylococcus aureus</i>	Fever, dyspnea, chest pain, hemoptysis	83	76	<i>Nocardia asiatica</i> (1)	Cotrimoxazole, 10 d Imipenem/ Amikacin, 14 d	18
2	F	18	<i>S aureus</i> , <i>Stenotrophomonas maltophilia</i> , <i>P aeruginosa</i>	Cough	65	70	<i>Nocardia asteroides</i> (1)	Cotrimoxazole, 6 mo Minocycline, 6 mo	36
3	M	12	<i>S aureus</i> , <i>Haemophilus influenzae</i>	Asymptomatic	62	69	<i>Nocardia</i> species (1)	No treatment	27
4	F	11	<i>P aeruginosa</i> , <i>H influenzae</i>	Asymptomatic	99	100	<i>Nocardia</i> species (1)	Cotrimoxazole, 6 mo	116
5	F	19	<i>P aeruginosa</i> , <i>S aureus</i>	Cough, dyspnea, fever	76	104	<i>N asteroides</i> (multiple)	Cotrimoxazole, 6 mo Minocycline, 1 mo	48
6	F	10	<i>S aureus</i> , <i>H influenzae</i> , <i>Candida albicans</i> , <i>Aspergillus fumigatus</i>	Asymptomatic	64	89	<i>Nocardia</i> species (1)	No treatment	84
7	F	26	<i>P aeruginosa</i>	Cough	51	61	<i>Nocardia elegans</i> (multiple)	Meropenem/ tobramycin, 14 d	17
8	F	28	<i>P aeruginosa</i>	Cough, dyspnea, fever, hemoptysis	47	40	<i>Nocardia farcinica</i> (1)	Cotrimoxazole, 6 mo	28
9	F	12	<i>P aeruginosa</i> , <i>S maltophilia</i> , <i>A fumigatus</i> , <i>Achromobacter xylosoxidans</i>	Cough	105	91	<i>Nocardia transvalensis</i> (2)	Cotrimoxazole, 14 d	5

Abbreviations: FVC, forced vital capacity; FEV<sub>1</sub>, forced volume in 1 second; F, female; M, male.

Therefore, clinicians are frequently faced with the isolation of a variety of pathogens that pose problems for deciding on the therapeutic approach to take. Moreover, simultaneous findings of numerous microorganisms often mean uncertainty as to which of them is exacerbating the process.

Microorganisms of the genus *Nocardia* are branching, and partially acid-alcohol-fast gram-positive bacilli. Numerous species have been described and are being reclassified continuously thanks to the use of molecular biology techniques. The species most commonly implicated in human respiratory disease are those that until a few years ago formed part of the *N asteroides* complex and which are now subdivided into different species: *N farcinica*, *Nocardia nova*, *Nocardia abscessus*, *N asteroides* sensu stricto, etc. Two of the species isolated in 2 of our patients have been described recently, *Nocardia asiatica* in 2004 and *N elegans* in 2005.

Nocardiosis is usually found in immunodeficient patients. Lung disease that alters local airway defense mechanisms is a known risk factor for nocardiosis. Nonetheless, nocardiosis has only been described sporadically in bronchiectasis and cystic fibrosis.

Ferrer et al<sup>11</sup> recently isolated microorganisms of the *N asteroides* complex in cultures from 40 patients. The most common underlying disease was bronchiectasis (80%), whether associated with cystic fibrosis or not. Of

TABLE 2  
 Possible Risk Factors and Clinical Course

Case	Corticosteroids		Antibiotics		Intravenous
	Oral	Inhaled	Inhaled Cycles/y	Oral Cycles/y	
1	No	No	Yes	3	1
2	No	Yes	Yes	6	No
3	No	Yes	No	Continuous	No
4	Yes (ABPA)	No	Yes	6	1
5	Yes (ABPA)	Yes	Yes	4	2
6	Yes (ABPA)	Yes	Yes	3	No
7	No	Yes	Yes	3	No
8	No	Yes	Yes	3	1
9	No	No	Yes	3	No

Abbreviation: ABPA, allergic bronchopulmonary aspergillosis.

the 12 patients with cystic fibrosis, 11 were colonized and 1 infected.

Few reports appear in the literature on nocardiosis in patients with cystic fibrosis<sup>11,15-17</sup> and review articles on infection in patients with cystic fibrosis make almost no reference to infection by this microorganism.<sup>3</sup> Likewise, few cases have been reported in children.<sup>16-18</sup>

Contrary to what has been reported, 56% of our series of 9 patients comprised pediatric cases, and females predominated. Curiously, cultures were negative for 2 patients in whom fiberoptic bronchoscopy was performed,

in 1 case for persistent fever and in the other to investigate a consolidation that was subsequently diagnosed as a new outbreak of allergic pulmonary aspergillosis.

The recommended first line therapy for nocardiosis is cotrimoxazole<sup>4,19</sup> and minocycline.<sup>20,21</sup> Imipenem-amikacin<sup>11</sup> and cotrimoxazole-amikacin<sup>10</sup> combinations have also been shown to be useful in treating such infections although the regimen must be adapted to the susceptibility of the species. Treatment from 6 to 12 months is recommended for lung infections. When cystic fibrosis is involved, the duration of treatment is less well defined. For serious infections, treatment might also last from 6 to 12 months in these patients; however, if symptoms are few, treatment may only last from 2 to 3 weeks, as in cases of exacerbations by other microorganisms. A pathogen that is a chance finding can be followed clinically and bacteriologically with a wait-and-see approach.

The course of nocardiosis has been favorable, both in cases reported previously and in the patients in our series.

In conclusion, a finding of *Nocardia* species in the sputum of patients with cystic fibrosis is rare and not always associated with active infection but rather with colonization, as occurs with other pathogens. The need for treatment should be evaluated on an individual basis depending on risk factors and clinical variables. The first line treatment is cotrimoxazole. Minocycline or, in more severe infections, imipenem and amikacin can be administered. The outcome of *Nocardia* species infection is not inevitably unfavorable.

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