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Nocardia cyriacigeorgica: pulmonary infection in a patient with Basedow—Graves disease and a short review of reported cases

Nocardia species are aerobic and saprophytic actinomycetes found all around the world. They invade the human body from the environment via trauma and the respiratory tract, and cause cutaneous, pulmonary, and systemic nocardiosis in humans. There is no age, ethnic group, or geographic variation in nocardiosis caused by the different *Nocardia* species, and the male to female ratio for infection is 3 to 1.[1] Nocardiosis is a rare infection and almost half of all cases are immunocompromised subjects.[2—7]

The taxonomy of *Nocardia* species is a complex issue and more than 30 different species have been reported to date.[8] The morphologic and phenotypic characterization of these species is difficult and time-consuming, hence they have been grouped mainly on the basis of their pattern of drug resistance (types I—VI). *Nocardia asteroides* drug pattern type VI has recently been identified as *Nocardia cyriacigeorgica* by use of the 16S rRNA gene amplification method. Therefore, *N. cyriacigeorgica* is not really a new species, but a new name given to a relatively common species.[9,10] This bacterium was originally described by Yassin et al. with the name *N. cyriacigeorgici*;[11] its name was subsequently changed to *N. cyriacigeorgica*.

Few invasive forms of *Nocardia* species have been reported in the literature.[12—22] The case described herein is the first in the literature involving pulmonary *N. cyriacigeorgica* infection in an immunocompromised patient with Basedow—Graves disease. We also review the previously reported cases of *N. cyriacigeorgica* infections in humans.

The case was a 37-year-old man who was started on propylthiouracil treatment, 450 mg daily, for treatment of Basedow—Graves disease. After approximately one year, an orbital computerized tomography (CT) scan was performed, and findings resembling a thyroid orbitopathy were found. He was started on methylprednisolone treatment, 96 mg daily, which was gradually tapered and ceased a month later; he developed diabetes mellitus secondary to corticosteroid treatment, which was controlled with appropriate diet and gliclazide treatment.

In July 2003 following consultation at the ophthalmology department, methylprednisolone treatment, 48 mg daily, was started once more. In September 2003, while under the corticosteroid treatment, he was admitted to

our hospital with complaints of lethargy, weight loss, muscle weakness, dyspnea, cough, hemoptysis, blurred and double vision, pain in the eye, generalized itching, and papular lesions on his upper trunk. On physical examination, crackles were detected in the basal segments of both lungs. Exophthalmia was detected in both eyes, diffuse and bilateral enlargement of the thyroid gland was noted, and muscle weakness was present in the lower extremities. A posteroanterior chest X-ray showed multiple sharp-edged homogenous masses as large as 6 cm in diameter resembling metastases, with heterogeneous increment in density in the lung parenchyma. In laboratory evaluation his leukocyte count was 12.8×10^9/l with 90% neutrophils in the differential count, C-reactive protein level was 9.62 mg/dl, and blood glucose level was 319 mg/dl. On the second day, he had a fever of 39.0 °C. In the chest CT, diffuse consolidations and calcifications were detected in the lung parenchyma. His blood glucose was regulated with insulin treatment.

Following consultation with the infectious diseases department and after obtaining a sputum specimen, cefepime 2 g iv every 12 hours, amikacin 1000 mg iv/day, trimethoprim–sulfamethoxazole (TMP–SMX 80/400 mg) four tablets every 12 hours po, and amphotericin B deoxycholate 1 mg/kg/day iv were started. Direct microscopic examination of the sputum with modified Ziehl–Neelsen stain showed many branching acid-fast bacilli (Figure 1). Sputum cultures performed on four occasions grew *Nocardia spp*, *Candida spp*, and *Aspergillus fumigatus*. Antibiotic susceptibility testing with the E-test revealed resistance to TMP–SMX (minimum inhibitory concentration (MIC) $\geq$0.064 mg/l) and his serum aspergillus galactomannan test was found to be negative; TMP–SMX and amphotericin B treatments were ceased and vancomycin was added. Following the determination of *Nocardia spp* as the causative agent this was changed to imipenem 500 mg iv (MIC 0.125 mg/l) every 6 hours for 5 days, but unfortunately the patient died. Although many attempts at treatment were undertaken, the patient's situation deteriorated. He died 30 days after hospitalization due to acute circulatory failure and disseminated infection that did not respond to medical treatment.

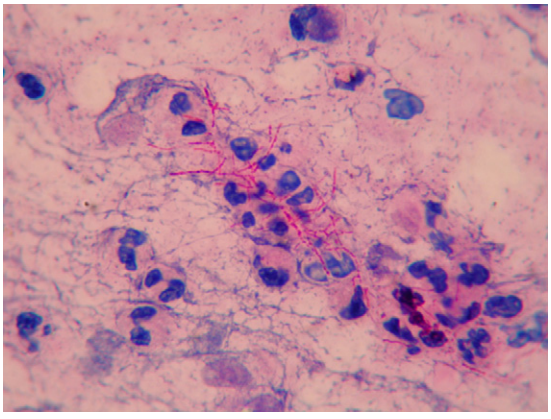

Figure 1 Modified Ziehl–Neelsen-stained direct preparation from sputum.

Our case was a male patient with an immunocompromising condition (Basedow–Graves disease), long-term and high dose corticosteroid usage, and resultant diabetes mellitus. Mootsikapun et al. reported four cases with diabetes mellitus and one case with Graves disease among their 70 cases of nocardiosis,[23] but there were no data on the species names of the bacteria. Our patient's symptoms, physical examination, and radiological findings were in concordance with the symptoms and findings of pulmonary nocardiosis reported in the literature.

A summary of reported nocardiosis cases with *N. cyriacigeorgica* as the etiologic agent is shown in Table 1.

Kageyama et al. reported 31 cases affected by *N. cyriacigeorgica* in Japan,[20] and in another report by the same author, 27 cases – 19 in Japan and eight in Thailand.[21] Poonwan et al. reported 13 strains of *N. cyriacigeorgica* in Thailand.[22] There were no data in these reports on the clinical features of the cases, hence these series could not be detailed in Table 1; we recommend the readers to see original reports for further details.[20–22]

In terms of geographical distribution, *N. cyriacigeorgica* seems to be predominant in Asian and European countries, as reported cases have come from Japan, Thailand, Turkey, Germany, and Spain.[9,13–23] In the literature, all reported cases have had the invasive disease, and there is only one case report on this bacterium in a cat with cutaneous infection.[24]

In our patient, after finding branching acid-fast bacilli on direct microscopy, sputum samples were cultured in blood agar, chocolate agar, and Sabouraud's dextrose agar, and incubated for 2–4 weeks. The diagnosis of Nocardia was obtained from our laboratory; the identification of *N. cyriacigeorgica* was performed by P. Boiron in the Mycology Laboratory of Claude Bernard University using the 16S rRNA gene amplification method.[9,25]

A total of 85 *N. cyriacigeorgica* cases have been reported to date for which 27 of the infections have been located in the lung, three in the brain, and one in the eye; the infection sites of the remaining 54 cases were not identified in the reports. According to Kageyama et al., the combination of an aminoglycoside with imipenem acts synergistically.[20] In the literature, most of the improved or resolved cases were treated with meropenem, amikacin, or ceftriaxone combination and oral TMP–SMX as maintenance therapy (Table 1); it appears that the most convenient combination is meropenem + amikacin. It should be noted that this bacterium is resistant to beta-lactams, ciprofloxacin, and some macrolides.[26] Our patient received a combination of cefepime, amikacin, and imipenem according to antibiogram test results. However, since he was seriously immunodeficient and diabetic due to long-term corticosteroid therapy, the condition resulted in death.

In conclusion, *N. cyriacigeorgica* has the potential to cause invasive infections in immunocompromised patients. Nocardia infections should be borne in mind in all cases with the probability of immune system derangement and should be differentiated from other fungal and mycobacterial infections and malignancies as quickly as possible and treated promptly with aggressive combination protocols.

Table 1 Summary of reported cases of *Nocardia cyriacigeorgica* infection (adapted from Ansari et al.[12])

Reference	Age (years), sex	Underlying disease and concurrent infections	Systemic corticosteroid use	Infection site	Culture samples	Treatment	Infection outcome
Yassin et al.[11]	NA	Chronic bronchitis	NA	NA	Bronchial secretion	NA	NA
Fux et al.[13]	59, M	RA	Yes + methotrexate, mycophenolate	Multifocal brain abscesses	Abscess fluid	Meropenem + amikacin + ceftriaxone, TMP–SMX	Resolved
van Dam et al.[14]	22, M	Fungal pneumonia + *N. farcinica*	No	Lung	BAL	Meropenem + amikacin, TMP–SMX	Improved
Barnaud et al.[15]	33, F	HIV infection	No	Brain abscess	BAL	Amoxicillin + minocycline + TMP–SMX	Improved
Elsayed et al.[16]	69, F	Diabetes mellitus, chronic lymphocytic leukemia	NA	Lung, CNS, RAM	Blood, adrenal biopsy specimen	Meropenem, TMP–SMX	Resolved
	47, F	Follicular non-Hodgkin lymphoma, ASCT	NA	Lung	Blood	Meropenem, TMP–SMX	Resolved (died from aspergillosis)
Alp et al.[17]	72, M	No	No	Multiple intracranial abscesses	Sputum, abscess material	Ceftriaxone + amikacin	Improved
Arslan et al.[18]	25, M	Behcet's disease	Yes	Lung, STA	Abscess material	Cefoperazone	Died (from pulmonary embolism)
Muñoz et al.[19]	74, M	COPD	Yes	Lung	NA	Sulfadiazine	Survived
	58, M	Heart transplant, diabetes	Yes	Lung	NA	TMP–SMX	Survived
	44, F	COPD, RA	Yes	Lung	NA	TMP–SMX	Survived
	71, F	COPD, lymphoma	Yes	Lung	NA	TMP–SMX	Died
	76, M	COPD	No	Lung	NA	TMP–SMX	Survived
	79, M	COPD	No	Lung	NA	Co-amoxiclav	Survived

NA, not available; M, male; F, female; RA, rheumatoid arthritis; TMP–SMX, trimethoprim–sulfamethoxazole; BAL, bronchoalveolar lavage; CNS, central nervous system; RAM, right adrenal mass; ASCT, allogeneic stem cell transplant; STA, soft tissue abscess; COPD, chronic obstructive pulmonary disease.

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