

Posttraumatic ankle arthritis due to a novel *Nocardia* species

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Abstract

Introduction Nocardial arthritis in immunocompetent patients is rare, and the optimum duration of antimicrobial therapy is unknown, although several months of antibiotic treatment is often recommended.

Case report We here report the first case of human infection with a novel *Nocardia* sp., summarise the epidemiology of nocardial arthritis and outline the feasibility of relatively short antibiotic treatments after careful surgical drainage.

Keywords Arthritis · Cotrimoxazole · *Nocardia* · Posttraumatic · Surgery

Introduction

Nocardia spp are aerobic Gram-positive bacteria that are considered to be ubiquitous soil saprophytes [1]. The genus encompasses more than 20 species [2], and new species are continuously being identified [2]. Human infections caused by *Nocardia* spp often appear as pneumonia [2] or disseminated diseases in severely immunocompromised hosts [1, 3]. Cotrimoxazole remains the antibiotic of choice [1, 3–7].

Nocardial arthritis in immunocompetent patients is very rare. Although no studies have compared the drainage procedure to the no-drainage procedure, the vast majority of experts recommend joint drainage in patients with septic arthritis [4]. In contrast, the duration of concomitant antibiotic treatment remains unknown only single case reports have been published.

We report here the first human infection with a novel *Nocardia* sp. that occurred as a posttraumatic arthritis in an immunocompetent host. We further discuss the feasibility of a relatively short antibiotic treatment after an adequate surgical drainage procedure and review the literature.

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Case report

A 40-year-old epileptic patient survived a car accident in the Rhone Valley, France, in May 2, 2008. He suffered open fractures (grade IIIb) of both ankles that were contaminated by earth, which were initially washed and then stabilised with intramedullar nailing. The patient received empirical antibiotic treatment of amoxicillin/clavulanate for 5 days. After his transfer to the Geneva University Hospitals, an elective surgical revision was necessary because of incongruence of the articular surfaces. On May

15, both intramedullar nails were removed, and the ankles were stabilised with external tibio-tarsal fixation devices (Hoffmann II) with the intention that these devices remain in place for 6 weeks. However, on June 19, the patient developed clinical signs of arthritis on his right ankle (erythema, tenderness, pain) with a purulent discharge of the scar. He had no concomitant fever, and the serum C-reactive protein level was 52 mg/L. All external fixation and thus all foreign material were therefore removed after 5 weeks, 1 week earlier than initially scheduled. The bone was considered to be sufficiently consolidated so that no new fixation was necessary on the infected ankle. The patient was given instructions on how to discharge his leg for another 2 months. Gram-staining and microscopic examination of the pus did not show any pathogen or crystal. The patient was empirically treated with intravenous vancomycin 2 g/day and ceftriaxone 2 g/day. Five days later, colonies of a *Nocardia* sp. appeared on microbiological cultures of the pus. The antibiotic treatment was changed to intravenous cotrimoxazole (160 mg trimethoprim/800 mg sulfamethoxazol; three times daily) for 5 days, followed by oral cotrimoxazole 960 mg (double-strength tablets) twice daily for a total of 8 weeks (until August 26). The fourth and last drainage performed on July 4 revealed that the surgical site was sterile. The cure was considered to be complete, and the patient has had no recurrence based on a follow-up at 20 months. No underlying immunosuppression was detected at that time.

Microbiology

Phenotypical diagnosis

The *Nocardia* were cultured on Columbia agar incubated aerobically at 35°C in an atmosphere enriched with 5% CO₂ [3, 8, 9]. Laboratory examination revealed beaded/branching, acid-fast, Gram-positive rods that were positive for β -lactamase, glucolysis and urease production. All tests for hydrolysis (casein, xanthine and tyrosine) were negative, as was the reduction of nitrate, growth at 45°C, fermentation of maltose and the test for esculin. The tests for casein hydrolysis involved a culture period of 14 days, those for xanthine, 3 weeks and those for tyrosine, 4 weeks.

Based on these phenotypical characteristics, the cultured *Nocardia* was classified as being closest to *N. beijingensis* [8, 9]. Antimicrobial minimal inhibitory concentrations (MICs) were determined by the *E* test (AB Biodisk, Solna, Sweden). The bacterium was susceptible to imipenem, tobramycin, kanamycin, tetracyclines and cotrimoxazole with corresponding MICs of 0.38, 1.5, 0.12, 0.064 and 0.25 mg/L, respectively.

Gene sequencing

The sequence of the 16S rRNA gene [10] was determined by a capillary sequence analyser (ABI 3130 XL DNA analyser; Applied Biosystems, Foster City, CA). Over a 979-bp fragment (region 49–1,027 of the 16S rRNA gene), our strain (GenBank Accession no. GQ281125) showed three nucleotide differences when compared to *N. beijingensis* [2] (GenBank Accession no. AF154129) and only one nucleotide difference with strains from Thailand and Japan [8] (DDBJ Accession no. AB094639–AB094656). Different sequences of *Nocardia* sp. and one sequence of *N. asteroides* (Accession no. Z82227) were also very close to our strain. Although sequence analysis of the 16S rRNA gene is adequate for the identification of numerous *Nocardia* sp., it is known that the speciation of some isolates requires the analysis of another gene target. The gene *seqA1* has been described as a more discriminative method [11]. With this approach, our clinical isolate had a *seqA1* gene showing at least 21 mismatches over 522 bp when compared to strains *N. beijingensis*, *N. arthritis* or *N. abscessus*.

Review of the literature

Table 1 summarises other clinical and epidemiological aspects of the 26 published cases of nocardial arthritis we identified in the English literature. In one-third of all cases, nocardial arthritis presented secondary to pneumonia, and in one-fourth it was related to a traumatic origin. The knee joint was involved in half of the cases, and most infections were due to *N. asteroides*. One-half of the patients were immunocompromised, and male patients predominated. Cotrimoxazole was used in two-thirds of cases, and the average number of surgical interventions per case was 2.3.

Discussion

We report here the first case of human infection with a novel *Nocardia* sp. that closely resembles *N. beijingensis* phenotypically. It clearly came from the soil that penetrated the open fractures of the patient. In a study carried out in 2001, *N. beijingensis* was detected in the soil around Beijing [2]. In 2004, microbiologists retrospectively identified 19 human cases of *N. beijingensis* infection in Japan and Thailand [8, 12]. Our phenotypical results are in agreement with the phenotypic characteristics reported in these earlier studies, with the exception of a negative growth test at 45°C, while the Asian study reported positive growth. Phenotypically, *N. abscessus* is frequently nitrate-positive and imipenem-resistant, *N. arthritis* is nitrate

Table 1 Arthritis (and concomitant infections) due to *Nocardia* spp in the English literature

Author	Publication	Sex	Age of patient (years)	Immunosuppression	Joint	Inoculation route	<i>Nocardia</i> spp ^b	Surgical drainage	Antibiotic (dose/day) ^c	Duration	Outcome
Moore et al.	Arch Dermatol Syphilol, 1951	Male	49	None	Knee	Trauma	<i>N. brasiliensis</i>	Drainage (1 ×)	Chlortetracycline 1,000 mg	Unknown	Cure
Baikie et al.	Lancet, 1970	Male	37	None	Lung knee	Pulmonary	<i>N. asteroides</i>	Arthrocentesis (2 ×) Drainage (1 ×) Disarticulation of knee	Sulfadiazine 6,000 mg Streptomycin 1,000 mg Cotrimoxazole 2,880 mg	3 months	Disarticulation of knee
Cruickshank et al.	Centr Afr J Med, 1975	Female	52	None	Ankle	Unknown	<i>N. asteroides</i>	Amputation	None	–	Amputation
Rao et al.	Arthritis Rheum, 1981	Male	52	Kidney transplant Acute rejection	Knee	Unknown	<i>N. asteroides</i>	Arthrocentesis (4 ×)	Cotrimoxazole 1,440 mg	6 months	Cure
Di Vittorio et al.	South Med J, 1982	Male	49	Leukemia	Lung elbow	Pulmonary	<i>N. asteroides</i>	Arthrocentesis (3 ×)	Sulfadiazine 6,000 mg	3 months	Cure
Clague et al.	J Rheumatol, 1982	Male	54	Alveolar proteinosis Prednisolone 15 mg/day	Lung ankle	Pulmonary	<i>N. asteroides</i>	Arthrocentesis (7 ×) Drainage (1 ×)	Amoxicillin 3,000 mg Sulfisoxazole 6,000 mg	3 months	Cure
Wilkerson et al.	Clin Orthop Relat Res, 1984	Male	32	None	Knee	Trauma	<i>N. asteroides</i>	Lavage (2 ×)	Mimocycline 150 mg Sulfisoxazol 6,000 mg Sulfisoxazol Mimocycline	3 months	Cure
Cons et al.	J Rheumatol, 1985	Male	19	Kidney transplant	Lung knee	Intra-articular injections Pulmonary	<i>N. brasiliensis</i>	Lavage (1 ×) Arthrocentesis (1 ×)	Cloxaciline Cefoxatime Cotrimoxazole 1,920 mg	3 months	Cure
Boudoulas et al.	Arch Dermatol, 1985	Female	56	Diabetes mellitus Hortons' Disease Prednisolone 20 mg/day	Lung knee	Pulmonary	<i>N. asteroides</i>	Arthrocentesis (7 ×)	Cotrimoxazole 7,680 mg intravenously	2 weeks	Not reported

Table 1 continued

Author	Publication	Sex	Age of patient (years)	Immunosuppression	Joint	Inoculation route	<i>Nocardia</i> spp ^b	Surgical drainage	Antibiotic (dose/day) ^c	Duration	Outcome
Robinson et al.	Bull Hosp Joint Dis Orthop Inst, 1989	Female	72	None	Hip arthroplasty.	Unknown	<i>N. asteroides</i>	Drainage (several) Removal of prosthesis	Cefazoline, Amikacin Micoocycline 200 mg Ofloxacin 100 mg	6 months	Cure
Freiberg et al.	Clin Orthop Relat Res, 1991	Male	11	None	Knee	Thorn	<i>N. asteroides</i>	Lavage (1×)	Cotrimoxazole 2,840 mg	3 months	Cure
Ostrum	Clin Orthop Relat Res, 1991	Female	51	Heart transplant	Lung hip	Pulmonary	<i>N. asteroides</i>	Lavage (1×)	Cotrimoxazole 1,920 mg	>30 months	Cure
Asmar et al.	South Med J, 1991	Male	9	None	Knee	Trauma	<i>N. asteroides</i>	Arthrocentesis (2×)	Cotrimoxazole	7 weeks	Cure
Torre et al.	Ann Rheum Dis, 1991	Male	75	Diabetes mellitus	Lung knee	Pulmonary	<i>N. caviae</i>	Arthrocentesis (several times)	Cotrimoxazole 1,920 mg Amoxicillin/clavulanic acid 1,500 mg	3 months	Cure
Koll et al.	Clin Infect Dis, 1992	Male	36	Cerebral astrocytoma Dexamethasone	Lung knee	Pulmonary	<i>N. brasiliensis</i>	None	Cotrimoxazole	(3 weeks) ^a	Death due to respiratory failure
Crouzet et al.	Rev Rhum Ed Fr, 1994	Male	45	Alcoholism Bronchial carcinoma Chemotherapy	Elbow	Unknown	<i>N. asteroides</i>	Arthrocentesis (2×)	Cotrimoxazole 1,920 mg	4 months	Cure Death due to cancer
Dinulos et al.	Pediatr Infect Dis J, 1999	Female	10	None	Knee	Animal aggression	<i>N. asteroides</i>	Arthrocentesis (3×) Lavage (3×)	Cotrimoxazole 1,440 mg Clarithromycin 500 mg	5 months	Cure
Arnal et al.	Lupus, 2000	Female	43	Systemic lupus erythematosus	Hip arthroplasty	Recurrence from lung infection	<i>N. nova</i>	Removal of prosthesis Lavage (2×)	Amikacin Imipenem 1,500 mg Amikacin 300 mg, erythromycin	3 months	Cure
Kahraman et al.	Transplant Proc, 2004	Female	30	Kidney transplant	Lung knee	Pulmonary	<i>N. asteroides</i>	None	Cotrimoxazole 1,920 mg	12 months	Cure

Table 1 continued

Author	Publication	Sex	Age of patient (years)	Immunosuppression	Joint	Inoculation route	<i>Nocardia</i> spp ^b	Surgical drainage	Antibiotic (dose/day) ^c	Duration	Outcome
Audenaert et al.	Acta Orthop Belg, 2004	Male	68	COPD-steroid therapy	Knee	Unknown	<i>N. farcinica</i>	None	Cotrimoxazole	6 months	Cure
Uçkay et al.	Abstract Swiss Annual congress of Infectiology Basel, 8–10 June 2005	Male	84	Diabetes mellitus Rheumatic polyarthritis Steroid medication	Knee	Trauma	<i>N. brasiliensis</i>	Lavage (1×)	Imipenem 2,000 mg Amikacin 1,000 mg Doxycycline 200 mg Linezolid 1,200 mg Cotrimoxazole 1,920 mg	3 months	Cure
Shah et al.	Scand J Plast Reconstr Surg Hand Surg, 2005	Male	46	Autoimmune disease Steroids	Wrist	Unknown	<i>N. asteroides</i>	Lavage (1×)	Cotrimoxazole 1,920 mg	Not reported	Cure
Shin et al.	Orthopedics, 2006	Male	82	None	Knee	Unknown	<i>N. asteroides</i>	Lavage (1×)	Cotrimoxazole 2,980 mg	6 months	Cure
Nizam et al.	J Orthop Surg (Hong Kong), 2007	Female	55	None	Knee-arthroplasty	Unknown	<i>N. nova</i>	Lavage (1×)	Cotrimoxazole 960 mg Clarithromycin 500 mg Amoxicillin/clavulic acid 1,750 mg	>24 months	Cure
Present article		Male	40	None	Ankle	Trauma	Novel species	Lavage (4×)	Cotrimoxazole 1,920 mg	8 weeks	Cure
Summary		Males 17/26 (65%)	Median age 48 years	Immunosuppression in 14/26 (53%)	Knee in 11/26 (42%)	Seeding from lung in 9/26 (35%); trauma in 27%	<i>N. asteroides</i> 17/26 cases (65%)	On average 2.3 surgical intervention per case	Cotrimoxazole in 18/26 cases (69%)	Median duration of 4 months for systemic and local arthritis infection	Cure without amputation in 22/26 cases (85%)

COPD, Chronic obstructive pulmonary disease

^a The patient died due to respiratory failure at 3 weeks of treatment^b *N. asteroides* group, not ubiquitously *N. asteroides* sensu stricto^c Reminder: a 1-day oral dose of two double-strength tablets of cotrimoxazole is 1,920 mg

positive and grows at 45°C and *N. beijingensis* is xanthine-positive. Our strain is also genetically close to *N. asteroides*, *N. abscessus* and *N. beijingensis* based on 16S rDNA sequencing [10], but substantial differences were documented in the *seqA1* gene [11], thus formally excluding *N. beijingensis*. We found no match for our strain in GenBank and related public databases. Therefore, we have to consider this isolate as a novel *Nocardia* species. With the widespread use of typing techniques and sequence-based confirmation of unusual isolates, it is likely that this novel strain will be encountered more than once in the future.

An important clinical message of this report is the feasibility of a rather short antibiotic therapy of only 2 months, provided that adequate surgical drainage or repetitive arthrocentesis has been performed. To date, treatments of several months are still recommended for nocardial arthritis due to the risk of recurrence [13] and substantial mortality in the case of disseminated disease [3, 14]. Our review of the literature revealed a median treatment duration of 4 months (with the exception of our treatment protocol), with one report of a 2-year treatment [6]; these treatments are ubiquitously associated with high cure rates of almost 90% (Table 1). Unfortunately, we were unable to answer the question of whether the continuous presence of a foreign body—i.e. infection of the joint prosthesis—with implant retention would influence the duration of the concomitant antibiotic treatment. Most nocardial arthritis cases involve native joints or joints with removed osteosynthesis material.

In systemic nocardiosis, the infection usually stems from the lungs of a severely immunocompromised host, and arthritis is typically related to haematogenous seeding [1, 3]. Consequently, prolonged antibiotic treatment durations are probably justified. In contrast, in immunocompetent patients with localised posttraumatic disease in the absence of a foreign body, one probably could combine adequate surgical drainage or arthrocentesis with a much shorter antibiotic course, as illustrated in this case, with 8 weeks of therapy, or in a previous case, with 7 weeks [15]. This combined regimen should reduce the adverse events of a prolonged cotrimoxazole therapy [7]. However, a careful follow-up is warranted when the duration of the antibiotic treatment is reduced, given the paucity of experience with this approach and the novelty of this and future strains. Randomised trials are very likely impossible due to the rarity of the disease, and further reports on the efficacy of relatively short-course antibiotic treatments are clearly warranted.

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The patient approved this case report by written signature.

Conflicts of interest statement None.

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