Case report

Septic arthritis due to *Nocardia brasiliensis* and a review of nocardiosis as a cause of arthritis

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**A R T I C L E   I N F O**

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**A B S T R A C T**

Bacteria of the genus *Nocardia* are implicated in several disease processes but are a rare cause of septic arthritis. Typically, the cause of *Nocardia* septic arthritis is dissemination from a pulmonary infection in an immunocompromised host. Herein we present a case of a 64-year-old male who had received a long course of prednisone for membranous nephropathy and developed a septic arthritis due to *Nocardia brasiliensis*. He was treated sequentially with trimethoprim-sulfamethoxazole and amoxicillin-clavulanate, linezolid and amoxicillin-clavulanate, tigecycline and amoxicillin-clavulanate, and omadacycline and amoxicillin-clavulanate. To our knowledge, only two prior cases of *Nocardia brasiliensis* septic arthritis without antecedent trauma to the joint or local skin breakdown have been reported. A review of the literature identified 19 other cases of *Nocardia* septic arthritis. This case reinforces the need to consider *Nocardia* infection in the differential diagnosis in the immunocompromised patient with concurrent pulmonary infection and septic arthritis.

**Introduction**

Bacteria of the genus *Nocardia* are rod-shaped Gram-positive bacteria that are ubiquitous in the environment. To date, 119 species of *Nocardia* have been described, with 40 of these being pathogenic in humans. The primary infection sites in humans are the lungs and the skin. Most cases of human nocardiosis have been reported in the immunocompromised, with diminished host immune response contributing to the dissemination of the organism [1]. Septic arthritis secondary to *Nocardia spp.* may arise in the setting of disseminated infection or cutaneous inoculation [2,3]. We report a rare case of *N. brasiliensis* septic arthritis and a literature review was conducted of the reported cases of septic arthritis due to *Nocardia* species.

**Case**

A 64-year-old male, presented with severe right knee pain for 10 days, with inability to ambulate because of the pain. His co-morbidities included gout, coronary artery disease, membranous nephropathy, with resultant stage 3 chronic kidney disease, type 2 diabetes, and hypertension. He had been treated with prednisone for his renal disease for four months prior to his presentation; his current dose was 20 mg/day, decreased from 60 mg/day that he had received for the prior month. He reported smoking marijuana but denied other illicit drug use. He worked as a landscaper and house painter but denied a history of penetrating trauma to the knee. He had no prior history of knee pain.

On admission, his WBC was 19.2 K/μL (reference range (RR) 4–10 K/μL), with 95.3 % neutrophils, 1.9 % lymphocytes, absolute lymphocyte count 365/μL (RR 900–3600/μL); and 1.6 % monocytes. His hemoglobin level was 10.8 g/dL (RR 11.5–14.9 g/dL), platelets 240 K/μL (RR 150–400 K/μL), and creatinine at baseline and on presentation was 1.44 mg/dL (RR 0.50–1.10 mg/dL). A urine protein/creatinine ratio performed a week before his presentation was 3.8 (> 3.5 is nephrotic range proteinuria), which had been improving with corticosteroid use. On physical exam, he was noted to have tenderness, erythema, and swelling of his right knee; an X-ray showed a moderate-sized joint effusion with diffuse soft tissue swelling and moderate-to-severe osteoarthritic change. An aspiration of the right knee was performed, and the synovial
fluid showed 64,000 white blood cells/mm³, with a 78% polymorphonuclear predominance, and calcium pyrophosphate crystals. A Gram stain of the synovial fluid showed gram-positive filamentous rods (1000×).

Table 1 Susceptibility testing of Nocardia brasiliensis isolate of case patient.

| Antibiotic                        | MIC, μg/mL | Interpretation |
|-----------------------------------|------------|----------------|
| Amikacin                          | 2          | Susceptible    |
| Amoxicillin + Clavulanic acid      | 12         | Susceptible    |
| Cefepime                          | > 32       | Resistant      |
| Ceftriaxone                       | > 64       | Resistant      |
| Ciprofloxacin                     | > 4        | Resistant      |
| Clarithromycin                    | 8          | Resistant      |
| Doxycycline                       | 4          | Intermediate   |
| Imipenem                          | 16         | Resistant      |
| Linezolid                         | 2          | Susceptible    |
| Minocycline                       | 2          | Intermediate   |
| Mexilfoxacin                      | 4          | Resistant      |
| Tobramycin                        | 1          | Susceptible    |
| Trimethoprim + Sulfamethoxazole   | 5          | Susceptible    |
| Tigecycline                       | 0.12       | No interpretive breakpoint |

Fig. 1. Photomicrograph of the Gram stain of the synovial fluid showing Gram-positive filamentous rods (1000×).

Fig. 2. Initial computerized tomograph of the lungs showing nodular and diffuse infiltrates.

Discussion

Forty species of Nocardia have been implicated as human pathogens [1]. Based on their biochemical properties and antimicrobial susceptibility patterns, the nocardiae are classified into various species complexes [3]. The Nocardia asteroides complex is the group clinically known to cause the vast majority of human Nocardia infections [4,5]. Distinct from this group is Nocardia brasiliensis, previously classified in the genera Streptothrix, Oospora, and Actinomyces. This species is distinct based on certain biochemical reactions, including nitrate reduction, urea hydrolysis, casein and tyrosine decomposition, and variable decomposition of hypoxanthine. Its distinctive drug susceptibility pattern is that of typical resistance to ciprofloxacin and clarithromycin,
and susceptibility to amoxicillin-clavulanate, trimethoprim-sulfa-
thiazole, and minocycline [5], although resistant strains may occur.

*Nocardia asteroides* is the most geographically widespread of the genus,
with most American cases of *N. brasiliensis* infection occurring in the
southeastern and southwestern USA [6]. *Nocardia brasiliensis* has been
rarely reported as a cause of septic arthritis [7].

Pulmonary involvement is the most common manifestation of
nocardiosis with underlying lung disease. In most cases, the acquired
immunodeficiency syndrome (AIDS), or long-term therapy with
cytotoxic agents and/or corticosteroids [9]. A low mean lymphocyte percentage 
≤ 7.8 % (RR 20–40 %) of the total

Table 2 provides a review of reported cases of *Nocardia* septic
arthritis without antecedent trauma. Of the 20 cases of *Nocardia* arthritis
without joint trauma, 40 % were due to *N. asteroides*, 20 % to
*N. farcinica*, 15 % to *N. brasiliensis*, 10 % to *N. cyriacigeorgica*, and single
cases ascribed to *N. pseudo brasilienensis*, *N. caviae*, and *N. nova*. This

### Table 2

| *Nocardia* species [Ref.] | Age/Sex | Risk factors | Joint | Other sites involved | Antimicrobial treatment/duration of therapy | Clinical outcome |
|--------------------------|---------|--------------|-------|----------------------|------------------------------------------|-----------------|
| *N. asteroides* [15]     | 30/F    | Renal transplant, on immuno-suppressives | Knee  | None                 | TMP-SMX/12 mos                           | Cure            |
| *N. asteroides* [16]     | 46/M    | Autoimmune disease, on corticosteroids | Wrist | None                 | TMP-SMX/unspecified Duration             | Unknown         |
| *N. asteroides* [17]     | 46/M    | HIV, IVDU    | Knee  | Pneumonia            | TMP-SMZ for 3 weeks, then minocycline/unspecified duration | Cure            |
| *N. asteroides* [18]     | 50/F    | Heart transplant | Hip   | None                 | TMP-SMX/> 30 mos                        | Unknown         |
| *N. asteroides* [19]     | 52/M    | Renal transplant | Knee  | Abscess on back      | TMP-SMX/6 mos                          | Cure            |
| *N. asteroides* [20]     | 56/F    | DM, temporal arthritis, on corticosteroids | Knee  | Pneumonia, pustules, tongue | TMP-SMX/2 weeks                        | Cure            |
| *N. asteroides* [21]     | 64/M    | CLL, with immune suppression | Knee  | None                 | Imipenem/cilastatin + TMP-SMX/unspecified duration | Death due to other cause |
| *N. asteroides* [22]     | 82/M    | corticosteroid to the joint, gout, osteoarthritis | Knee  | None                 | TMP-SMX/6-12 mos                        | Unknown         |
| *N. farcinica* [23]      | 55/M    | HSCT, steroid-dependent chronic GVHD; DM, chronic renal failure | Knee  | None                 | Ceftriaxone/levoflox, 7 days; meropenem/amikacin, 15 days; meropenem/levoflox, 10 days; linezolid, days 35–52; levoflox/minocycline, 5 mos; clinical failure; then ticarcillin-clavulanate/TMP-SMX until day 172, cefuroxime/TMP-SMX for 6 mos, then addition of doxycycline | Death due to other cause |
| *N. farcinica* [24]      | 68/M    | DM, COPD, on corticosteroid | Knee  | Pneumonia, pleural effusions | TMP-SMX/6 mos                           | Cure            |
| *N. farcinica* [25]      | 78/M    | Not specified | Knee  | Pneumonia            | TMP-SMX/11 days                         | Death from respiratory failure |
| *N. farcinica* [26]      | 82/M    | DM, Pneumocooniosis | Knee  | Right empyema, Cutaneous vesicles | Leovoflox/6 mos                         | Cure            |
| *N. brasiliensis* [27]   | 4/F     | None         | Knee  | Proximal IP joint    | TMP-SMX/6 mos                          | Cure            |
| *N. brasiliensis* [28]   | 36/M    | Astrocytoma, on dexamethasone | Knee  | Pneumonia            | TMP-SMX/amikacin/20 days                | Death from respiratory failure |
| *N. brasiliensis* [this case] | 64/M | Membranous nephropathy, on corticosteroids; DM, gout | Knee  | Pneumonia            | TMP-SMX/amox-clav, 21 days; linezolid/amox-clav, 14 days; tigecycline/amox-clav, 42 days; omadacycline/amox-clav, 6 mos | Cure            |
| *N. cyriacigeorgica* [29] | 38/F   | SLE, on immuno-suppressives | Knee  | None                 | TMP-SMX/12 mos                          | Cure            |
| *N. cyriacigeorgica* [30] | 60/M   | HSCT, acute GVHD | Knee  | None                 | Imipenem/amikacin, 1 mos; cefuroxime/doxycycline, 1 year | Cure            |
| *N. pseudo brasilienensis* [31] | 86/M | Aortic valve replacement; pacemaker; stress fracture of the leg | Knee  | None                 | TMP-SMX/ciprofloxacin/unspecified duration | Cure            |
| *N. caviae* [32]         | 75/M    | Osteoarthritis, DM | Knee  | None                 | TMP-SMX/amox-clav for 1.5 mos, then amox-clav for 3 mos Imipenem for 15 days, followed by imipenem/ceftriaxone until day 39, then ceftriaxone/TMP-SMX until day 80, followed by amoxicillin/clarithromycin until death | Death due to other cause |
| *N. nova* [22]           | 64/M    | DM, lymphoma in remission, myasthenia gravis, on immune suppression | Knee  | None                 | Cure                                    | Death due to other cause |

**Abbreviations:** Amox-clav, amoxicillin-clavulanate; CLL, chronic lymphoid leukemia; DM, diabetes mellitus; GVHD, graft versus host disease; HSCT, hematopoietic stem cell transplant; IP, interphalangeal; levoflox, levofloxacin; SLE, systemic lupus erythematosus; TMP-SMX, trimethoprim-sulfamethoxazole; IVDU, Intravenous drug use.
showcases the rarity of *N. brasilienensis* as a cause of septic arthritis. The cases were reported in patients 30–86 years of age; 75 % occurred in men. Seventy-five percent of the involved patients had undergoing immunosuppression, either from corticosteroid use (as in this case), organ transplantation, or HIV infection. Seventeen of the 20 cases involved the knee joint with involvement of the wrist, the hip, and small joints of the hand reported as well. Six of these cases had concomitant pulmonary involvement, indicating the need to assess other sites for *Nocardia* infection if there is joint involvement, as was noted in our case. In terms of therapy, trimethoprim-sulfamethoxazole was the mainstay of treatment; in 90% of cases this agent was employed as monotherapy or in combination with other antibiotics. Forty percent of case patients received 8–12 months of therapy; our patient received 9 months. In one case, clinical cure was documented after only two weeks of therapy [20]. Cure was achieved in 55 % of the cases (11 out of 20 cases, including this case), with death due to other causes occurring in 25 % of cases prior to treatment completion; no outcome was reported in 20 % of the cases. No deaths were ascribed to nocardiosis.

Increasing levels of resistance are known for *N. farcinica* and resistance to TMP-SMX and sulfonamides has been reported across all *Nocardia* species [31]. Minimum inhibitory concentrations of tigecycline are noted to be generally 1–2 dilutions within the 100 % inhibition omadacycline minimum inhibitory concentration values for non-tuberculous mycobacteria, indicating that this could be an alternative regimen for treatment [32], prompting its use in our patient.

*Nocardia* infections are known in literature to primarily occur in immunocompromised individuals. *Nocardia* species known to disseminate to various body sites, including the central nervous system. However, there have been infrequent instances of isolated *Nocardia* joint infections, without a previous history of penetrating trauma to the joint, or local cutaneous disruption. We highlight the importance of considering this diagnosis, especially in the setting of an immunocompromised patient. It is imperative to follow cultures until finalization, as diagnostic yield is significantly increased with longer incubation times, even up to 4 weeks [30]. A high degree of suspicion for nocardiosis is indicated if there is initial Gram stain evidence of filamentous gram-positive rods in a clinical specimen.

**Ethical approval**

The patient was treated with the standard of care. No research studies were conducted. Thus, the study does not require Institutional Review Board Approval.

**Consent**

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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