Skin Infections Caused by *Nocardia* Species

A Case Report and Review of the Literature of Primary Cutaneous Nocardiosis Reported in the United States

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Abstract: Nocardiosis is an uncommon infection caused by *Nocardia* species, a group of aerobic actinomycetes. Disease in humans is rare and often affects patients with underlying immune compromise. Acquisition of this organism is usually via the respiratory tract, but direct inoculation into the skin is possible, usually in the setting of trauma. We report an encounter of a previously healthy man, with cellulitis and abscess formation of the upper arm. The organism isolated from the wound culture was a partially acid-fast, Gram-positive rod, identified as *Nocardia* species. Our patient recovered after 6 months of treatment with trimethoprim-sulfamethoxazole. Along with our case, we reviewed the profile of patients with primary cutaneous nocardiosis reported in the United States between 1985 and 2010. We emphasize that *Nocardia* infection should be considered in the differential diagnosis of skin lesions especially if a person has a history of trauma or failed prior antibiotic therapy.

Key Words: *Nocardia*, nocardiosis, cutaneous, skin, infection

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Nocardiosis is a rare infection caused by different species of the genus *Nocardia*. It usually causes pulmonary disease or central nervous disease in immune-compromised hosts.[1] The disease can also affect the skin and subcutaneous tissue in a smaller percentage of cases. Cutaneous nocardiosis can be divided into primary cutaneous nocardiosis and secondary cutaneous nocardiosis (usually after dissemination from the lungs).[2] Primary cutaneous nocardiosis is relatively rare and is characterized by 1 of 3 clinical manifestations: superficial skin infections (ie, abscesses, cellulitis, ulceration, and pustules), lymphocutaneous type (including cervicofacial variant in children), and nocardial mycetoma.[3] The goal of this article was to present a rare case of primary cutaneous nocardiosis, followed by a review of primary skin manifestation of nocardiosis in the United States from 1985 until 2010.

CASE REPORT

The patient was a 34-year-old, previously healthy man, a biochemical bioterrorism researcher in West Virginia. One week before his first visit to our hospital, he was working in a family member's basement. He had been fitting fiberglass insulation and doing plumbing work. Hot water dripped on his arm while soldering pipes. Two days later, he noticed 2 white spots on the left arm. He started squeezing those pustules, and some pus was discharged. He cleaned the area with soap, water, and peroxide. He thought he may have had a splinter there, so he punctured the lesions with a needle to remove it. Later, erythema and swelling appeared in the region surrounding the 2 spots. On November 21, 2008, he presented to our emergency department complaining of pain, redness, and swelling of the left arm. A culture from one of his abscesses was sent for analysis. The patient was then discharged home with a prescription of trimethoprim-sulfamethoxazole (Bactrim) (TMP-SMX) for a suspected staphylococcal skin infection. However, increased pain in his left arm and the presence of chills prompted him to return to the emergency department 2 days later.

Upon admission, he was afebrile (98.3°F); he had a pulse of 81 beats/min, respirations of 16 breaths/min, and a blood pressure of 164/85 mm Hg. His review of systems was unremarkable. Skin examination showed marked erythema in the left arm with diffuse margins and 2 sizable abscesses distributed on the inner aspect of the arm; the size of the larger one was 1.5 × 2 cm, whereas the other one was 1 × 0.5 cm. Streaks of lymphangitis radiated as far as the anterior surface of the forearm. There were no nodules beneath the skin, lymphadenopathy, or edema. Draining pus was expressed on pressure of the abscesses (Fig. 1).

Laboratory data showed mild leukocytosis of 14,400/μL consisting of 79% neutrophils. The hemogram was normal, as were blood chemistries. The patient had incision and drainage of one of the abscesses, and material was again sent for culture. Hospitalization was recommended for intravenous antibiotics, and vancomycin was administered. The blood cultures obtained at admission were sterile. On Gram staining, the smear of the purulent discharge collected from the abscess at the initial visit revealed weakly gram-positive, beaded, branching filaments. A modified acid-fast stain (Ziehl-Neelsen) was positive. The wound culture yielded *Nocardia* species 3 days after the start of incubation. Further speciation was not performed in our laboratory. *Nocardia* skin and soft tissue infection was diagnosed.

After the culture showed *Nocardia* species, the treatment was switched to oral double-strength TMP-SMX tablets twice daily. On hospital day 5, the soft-tissue infection and leukocytosis improved. Our patient was discharged on oral TMP-SMX 2 tablets twice daily. Follow-up was continued with an infectious disease specialist in West Virginia. He continued the same regimen for nearly 6 months because of a persistent small lesion that resolved upon completion of treatment.

EPIDEMIOLOGY AND GEOGRAPHIC DISTRIBUTION

Nocardiae are known as aerobic actinomycetes. The organisms are gram-positive, bacillary, branching bacteria. The members of the genus *Nocardia* are found worldwide in the soil, water, dust, and decaying vegetation.[3,4] The first case of nocardiosis was described by Edmond Nocard in 1888 in cattle with bovine farcy (lymphadenitis). In 1890, Epinger reported the first human infection with *Nocardia* species in a man with a pleuropulmonary disease, cerebral abscesses, and meningitis.[5] Since then,

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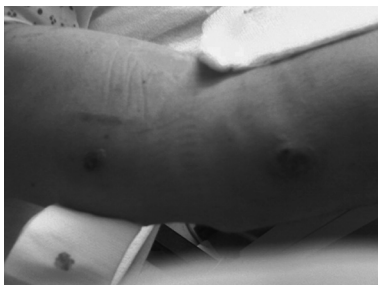

FIGURE 1. Appearance of the patient arm at the time of admission. Cellulitis and abscesses were noted.

a large number of species have been described within the genus *Nocardia*. Recent taxonomic reviews cite as many as 32 valid *Nocardia* subspecies of human clinical significance. Of these, the most commonly encountered are *Nocardia asteroides*, *Nocardia brasiliensis*, *Nocardia farcinica*, and *Nocardia otitidiscaviarum*.[3,4] *Nocardia asteroides* accounts for 90% of nocardial infections in the United States and usually presents as pulmonary or disseminated disease.[3,6–8]

The incidence of nocardiosis in the United States was thought to be between 500 and 1000 new cases each year.[1] At present, infections with *Nocardia* species are being reported more than in previous years. This may be related in part to the utilization of more responsive diagnostic approaches, more people are on immunosuppressive therapy, or perhaps physicians are more aware of this particular organism.[3,9,10] The best data on the sites of *Nocardia* infection come from a 1994 literature review of 1050 cases of nocardiosis: 71% of reviewed patients had pulmonary or systemic nocardiosis, whereas only 8% had primary cutaneous disease.[11]

In our case, *Nocardia* species was identified in an immunocompetent patient in whom this organism was accidentally inoculated into the skin. Primary cutaneous nocardiosis was therefore diagnosed; a review of the literature since 1985 revealed an additional 75 cases of primary cutaneous nocardiosis reported in the United States. Demographic and clinical data from all cases are summarized in Table 1. In general, most cases of primary cutaneous nocardiosis are caused by *N. brasiliensis,* and in this form, it is commonly a disease of immunocompetent patients.[2,10–12] In our review, *N. brasiliensis* was found in 49 cases, followed by *N. asteroides* (16 cases). In addition, 5 cases had other subspecies identified (Table 1).

The geographic distribution of the 75 cases included in this article can be seen in Figure 2. A worthy review of earlier *N. brasiliensis* cases was made by Smego and Gallis in 1984. They found 62 cases of disease caused by *N. brasiliensis* in the United States, of which 46 had infections of the skin and soft tissue. They reported 63% of case reviews as coming from Texas, North Carolina, California, Oklahoma, and Florida, which is similar to our case distribution. In particular, we found almost half of our cases in Texas; as opposed to the study by Smego and Gallis,[10] we also found a fairly large number of cases in the Northeast.

The infective process in primary cutaneous nocardiosis is usually initiated by local trauma, such as puncture wounds. *Nocardia* is one of the saprophytic bacteria that can be found on different materials and can be implanted into puncture wounds. In our review, 45 patients remembered having some sort of trauma. Some examples include puncture wounds secondary to rose thorns,[12] a splinter from commercially treated lumber,[13] cat scratches,[14] insect bites,[15,16] or even tick bites.[17] At increased risk are gardeners[18,19] or those individuals who perform outdoor activities[6,20]; others had some sort of contact with the soil after falling or other accidents.[21,22] Pediatric cases have been described as early as 7 months of age.[15] Infection in immunosuppressed individuals is frequent, but there is no definite correlation with the degree of immunosuppression. Of the 72 cases in which information was available, 28 patients were immunocompromised, whereas 44 cases occurred in normal hosts. Risk factors associated with nocardial infections included use of corticosteroids

TABLE 1. Cases of *Nocardia* Infections Reported in the Literature Between 1985 and 2010

Characteristic	No. Cases (%)	No. Cases With Missing Information
All cases	75 (100)	—
Sex		7
Male	44 (65)	
Female	24 (35)	
Age, y		7
0–20	22 (32)	
20–40	12 (18)	
40–60	11 (16)	
60–80	17 (25)	
>80	6 (9)	
Infection site		7
Upper extremities	26 (38)	
Lower extremities	23 (34)	
Head	10 (15)	
Other	3 (4)	
Multiple sites	6 (9)	
Immunological system		3
Compromised	28 (39)	
Competent	44 (61)	
Trauma		12
Yes	44 (70)	
No	19 (30)	
Nocardia species		5
N. brasiliensis	49 (70)	
N. asteroides	16 (23)	
N. otitidiscaviarum	2 (3)	
N. transvalensis	1 (1)	
N. nova	1 (1)	
N. farcinica	1 (1)	

FIGURE 2. Geographic distribution of the 75 cases of primary cutaneous nocardiosis reported in the United States between 1985 and 2010.

(8 cases), autoimmune disease such as myasthenia gravis, sarcoidosis, rheumatoid arthritis, temporal arteritis, and ulcerative colitis. Other predisposing conditions included diabetes mellitus (7 cases), hematologic and other malignancies (8 cases), and transplantation (5 cases), and 2 patients were HIV positive. Our patient had a history of working in a basement and punctured his arm with a needle. He was previously healthy. This picture fits the general description of acquiring *Nocardia* species into the skin.

CLINICAL VARIANTS

Primary cutaneous nocardiosis can mimic other superficial skin infections caused by more common organisms, such as staphylococci and streptococci. Because of this, nocardiosis can often be misdiagnosed. Cutaneous nocardiosis can present in different forms: superficial skin infections, lymphocutaneous infections, or deeper infections (ie, mycetoma). The 2 acute forms are the superficial and lymphocutaneous infections.[10,23,24] When the 3 types of disease are compared (Table 2), the superficial type is more frequently seen (43 cases). The most common form found in the United States is that of superficial skin infections such as cellulitis,[15,25] ulcers,[22,26] pustules,[16] papules,[6] plaques,[8] granulomas,[27] and abscesses[7,28] as also illustrated in our case report. Superficial cutaneous abscesses may rarely disseminate to other areas including bone, muscle, and joints. Ng and Hellinger[7] reported a case of superficial cutaneous *N. asteroides* with dissemination to the brain. Compared with the other cutaneous forms, superficial skin infection is the least serious of the localized infections.[24] It usually involves some form of trauma with contamination of the wound. Immunocompromise is not a necessity, as described by Fergie and Purcell[15] in a report of 31 cases of cutaneous *N. brasiliensis* in children from South Texas.

The lymphocutaneous type of infection[12,14,29–31] was the second most common form encountered in our review (Table 2). Worldwide, it is the least common form of primary cutaneous nocardiosis. Lymphocutaneous forms present with 1 or more cutaneous nodules at the site of inoculation, followed by lymphangitis and regional lymphadenopathy. It is also known as sporotrichoid nocardiosis.[10,23,24] In our reviewed cases, there was a mix of immunocompromised (46%) and immunocompetent patients (54%). Notably, more than 70% of the patients were male. Most of the lesions initially involved the upper extremities, and traumatic inoculation of *Nocardia* was present in more than 70% of the cases. This reinforces the importance of skin inoculation of *Nocardia* in contact with soil-contaminated material.[23] When identified, the most common *Nocardia* species was *N. brasiliensis*. It appears more virulent than *N. asteroides*. An atypical cervicofacial variant of the disease has been reported in children. There is no history of a skin wound or trauma, and children develop a pustule in the nasolabial area followed by cervical adenopathy, fever, and systemic symptoms.[23] In the reviewed cases, we also found cervicofacial nocardiosis reported in 2 male adults. Both of the patients were imunocompromised. *Nocardia brasiliensis* was isolated in 1 patient, whereas *N. asteroides* was found in the other case.[32,33]

Mycetoma or Madura foot is a chronic form of cutaneous nocardiosis. It is a deep, granulomatous, progressively destructive infection of the underlying soft tissues with extension to bone. These lesions are chronic and indurated and appear as areas of localized "tumor-like" swelling with sinus tracts.[10,23,34] Worldwide, mycetoma is the most common cutaneous manifestation of *N. brasiliensis*. This form is relatively rare in the United States, and it is more frequently found in patients living in US Border States, such as Texas. In our review, the mycetoma cases

TABLE 2. Comparison Among the 3 Types of Primary Cutaneous Nocardiosis

Characteristic	Superficial	Lymphocutaneous	Mycetoma
All cases	43	26	6
Species			
N. brasiliensis	29	19	1
N. asteroides	10	3	3
Other/no speciation	4	4	2
Trauma			
Yes	25	16	3
No	12	6	1
Immunocompromised			
Yes	14	12	2
No	27	14	3
Duration prehospitalization, wk			
Mean (min-max)	12.73 (0.5–52)	20.6 (0.5–208)	253.3 (40–624)
Medical treatment			
TMP-SMX alone	16	8	4
Sulfonamide alone	2	5	0
TMP-SMX in combination	0	7	2
Sulfonamide in combination	3	0	0
Other	14	5	0
Surgical treatment			
Yes	16	14	2
No	21	10	4
Duration of treatment, mo			
Mean (min-max)	4 (1–12)	3 (0.5–6)	13 (6–20)

came from Florida, California, Texas, Louisiana, and North Carolina.[20,34–37] Most of the patients had a history of exposure to either soil or trauma. The usual sites involved were the hands and feet. There are also documented cases in Mexico where farm laborers develop mycetomas on their back and shoulders, secondary to carrying soil-contaminated loads.[10] Lum and Vadmal[36] reported a nocardial mycetoma in an immunocompetent woman with no history of trauma. The infection was also localized on her back. Finally, reported cases of mycetoma appear to have a more indolent disease course ranging from months to years (Table 2).

DIAGNOSIS AND THERAPY

Primary cutaneous nocardiosis will remain a challenging diagnosis. The organism can be correctly identified if appropriate specimens are collected. Smear and culture remain the most important methods of diagnosis.[3] *Nocardia* can be seen using Gram, Ziehl-Neelsen, and modified Kinyoun stains. The modified acid-fast stain should be used to confirm the acid fastness of the organisms detected by Gram staining. The organisms appear as gram-positive, branching, filamentous rods.[10] The organism can grow on media for bacteria, fungi, or mycobacteria. Forty-two (95%) of 44 cases with culture reported positive results. Saubolle and Sussland[3] found a similar number in their nocardiosis review. It should be noted that the growth is slow, and media should be examined for up to 2 weeks for possible slow-growing *Nocardia*.[5] In the reviewed cases, the positive colonies of *Nocardia* were visible after 2 to 7 days. Tissue histological evaluation could prove important as well. Biopsy of 19 specimens in the review helped in narrowing the differential diagnoses. Biochemical testing and antibiotic resistance patterns can differentiate some species of *Nocardia*, but final determinations are best accomplished with different molecular techniques such as 16S rRNA sequence analysis or polymerase chain reaction.[3,9] Speciation can have an increasingly important impact, given the changing susceptibility patterns of different species.

Treatment of cutaneous nocardiosis requires antimicrobial therapy and, whenever possible, surgical debridement and drainage. Sulfa-containing antimicrobials are still the treatment of choice, and TMP-SMX is frequently used in treating skin infections due to different subspecies of *Nocardia*. Other effective drugs are cephalosporins, imipenem, minocycline, and clindamycin.[5] No prospective studies have been done evaluating the efficacy of TMP-SMX compared with other antibiotics. In the cases reviewed, most cutaneous nocardiosis responded well to TMP-SMX alone or in combination (56% of the treated cases). In general, TMP-SMX was well tolerated. Only a minority of the cases showed allergy or intolerance to sulfonamide (7 cases).

Most authors advise treating cutaneous forms for 1 to 3 months. It is postulated that the treatment should be prolonged because of the number of relapses after short courses of therapy,[5,38] The reported duration of therapy for nocardial infection ranged from 1 week for minor infections to more than a year for complicated ones (Table 2). Immunocompromised patients who have primary cutaneous nocardiosis are similarly treated. Appropriate surgical drainage of suppurative cutaneous infections should be done in the appropriate clinical setting.[23]

Clinical outcome is good in cutaneous nocardiosis. All the 54 reported patients with soft-tissue nocardial disease, for whom outcome was available, recovered after treatment. Two patients died of AIDS complications.

CONCLUSIONS

Nocardiosis is a rare disease, and it is frequently misdiagnosed. *Nocardia* infection should be considered in the differential diagnoses of a skin and soft tissue infection, especially if there is a history of trauma, or the infection fails to respond to initial antibiotic direction. When cultures are sent, and the microbiology laboratory is alerted, the organism is commonly recovered. Patients with primary cutaneous infections appear to recover well, but prolonged treatment may be needed.

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