Original Article

Nocardia brasiliensis Infection Seen on Grafted Skin of the Dorsum of a Foot

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Abstract

For the past 4 years a 23 y-old female has noticed erythema on the dorsum of the right foot, where skin was grafted due to a traffic accident 20 years ago. She visited the Department of Dermatology of Gifu Prefectural Hospital on Oct. 19, 1998; her general health was good. Physical examination disclosed a swelling with erythema, papules and pustules on the dorsum of the right foot. The results of routine laboratory investigations were within normal limits except for the white blood cell count (11,300/mm³), blood sediment rate (25 mm/hrs), C reactive protein (1.21) and rheumatoid factor ($\times 16.6$). Several yellowish and verrucous or wrinkled colonies were grown on Sabouraud's agar culture from the biopsied specimen of the foot.

Histopathological features showed epidermal hyperplasia with elongation of rete ridges and granulomatous changes in the dermis; many mononuclear and giant cells were present, and several positive fine filamentous and irregularly branching structures with PAS and Grocott stains were seen in the granulomatous nests. Both clinical and histopathological features led to speculation of *Nocardia* infection, and *Nocardia brasiliensis* was determined. The patient was treated by surgical total resection including the grafted skin. Although a soybean-sized nodule was seen on the border of the skin-graft of the foot three months later, there was no recurrence after the local resection.

Key words: *Nocardia* infection, histopathology, *Nocardia brasiliensis*

Introduction

Primary nocardiosis is well known as a gram-positive, partially acid-fast bacterial infection developing in the lungs, central nervous system or other parts of the body¹⁾, often in association with collagen diseases such as systemic lupus erythematoses²⁾ or leukemia³⁾, which occur opportunistically. Although several cases of *Nocardia* infection have been reported^{4–14)}, sometimes the diagnosis is difficult, because *Nocardia* is thought to be one of the bacteria which causes opportunistic infections. We report an interesting case of *Nocardia* infection, primary lymphocutaneous and mycetoma nocardiosis seen on the grafted skin of the dorsum of the foot, which was confirmed

histopathologically by Grocott staining, cultured colony appearance on the slant medium, and cell wall and dissolution analysis of the strain. Additionally, cases of cutaneous nocardiosis due to *Nocardia brasiliensis* (*N. brasiliensis*) reported in Japan are reviewed.

Case Report

A 23 y-old female had a 4 to 5 year-history of nodules and plaques on her right leg, which was treated with a skin graft following a traffic accident when she was 2 years old. She visited the Department of Dermatology of Gifu Prefectural Hospital because of swelling with erythema on the dorsum of the left foot on Oct. 19, 1998. Walking did not worsen the swelling. She was in good general health, and there was no special family history. Physical examination disclosed brownish verrucae and suppurative nodules on the dorsum of the foot (Fig. 1a & b), and a larger

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Fig. 1. a; Clinical features of the right dorsum of a 23y-old female. Granulomatous nests with swelling and pustules were seen. b; Lateral view of the lesion. c; A granuloma near right inguinal lesion. d; A white yellowish colony on Sabouraud's slant dextrose agar medium obtained from the dorsum of the right foot. e; A giant verrucous colony on Sabouraud's dextrose agar medium (biopsied from the inguinal lesion). f; Histopathological features of the lesion; Several granulomas with bacterial elements surrounded by many mononuclear cells with giant cells were seen in the dermis (PAS stain). g; Tubulous branching elements positive with Grocott stain were seen in the granuloma.

nodule was seen near the right inguinal region (Fig. 1c); several tender lymph nodes were palpable in this region.

Results of routine laboratory investigations showed the white blood cell count to be above normal ($11,300/\text{mm}^3$) and blood sedimentation rate

(BSR) was relatively elevated (25 mm/hrs). C reactive protein (CRP) was 1.21, and the rheumatoid factor was positive ($\times 16.6$). However, there were no abnormalities in the immunological examination including antinuclear antigen (ANA), or immunoglobulins G, A & M and CD subset markers (CD4; 61.7, CD8; 28.9). Physiological examination, including electrocardiogram and chest X-ray film, was within normal limits.

Sporotrichosis and actinomycetoma were initially suspected, however, there were no fungal elements in the 20% KOH sample of the scales from the lesion. Some kind of bacterial infection with granuloma was also suspected, so that she was initially treated with a 2-month course of oral cephalosporin, 500 mg three times daily, followed by a 2-month course of ofloxacin, 100 mg three times per day, which produced relatively good effects. Several yellowish white and verrucous or wrinkled colonies with moist surface were grown on Sabouraud's slant agar from the biopsied specimen of the foot (Fig. 1d). The colonies showed reddish colored feature on the backside. Additionally, small dark orange-colored colonies with moist surfaces were grown on Ogawa's agar from the biopsied specimen of the inguinal nodular lesion, which was later inoculated onto Sabouraud's giant agar medium for further observation (Fig. 1e). However, after 4 months, there was no decrease of the tumor-size, and on Feb. 23, 1999, total resection of the lesion including a nodule on the right upper leg was carried out with a skin graft. Again, small specimens were cultured onto Sabouraud's agar medium and several colonies of bacteria similar to those in Fig. 1d were grown on the medium.

Histopathological features of the biopsied specimen from the dorsum of the foot included epidermal hyperplasia with elongation of rete ridges and a cyst was seen in the dermis, perhaps induced by the skin graft. There were several granulomatous lesions with nests of the bacterial element surrounded by many mononuclear cells and giant cells in the dermis (Fig. 1f). Higher magnification of these granulomas showed several positive substances with Grocott stain (Fig. 1g) as well as PAS stain, which consisted of fine filamentous and irregularly branching components. Histological examination and culture were consistent with nocardiosis. After a detailed investigation on the properties of the cell wall, and a dissolution test of the isolated organism such as casein, hypoxanthine, tyrosine and xanthine and sugar availability (inositol and galactose), *N. brasiliensis* infection was determined.

Oral administration of sulfa derivatives as well

Fig. 2. Relationship between *Nocardia* species and clinical forms of nocardiosis.

as tetracycline was not successful due to side effects of nausea and vomiting or dizziness. Although a soybean sized nodule was seen on the border of the grafted skin of the foot three months later, there was no recurrence after the local resection.

Discussion

Primary cutaneous nocardiosis is uncommon and occurs mainly in immunosuppressed situations^{2,3)} such as bone marrow transplantation, AIDS, post-operative complications or after localized trauma⁵⁾, and cancer⁷⁾. Infection with *Nocardia* species is an increasingly recognized complication of solid organ transplantation. *N. asteroides* accounts for most transplant-related nocardiosis, while *N. brasiliensis* rarely causes infection in organ transplant recipients⁶⁾.

N. brasiliensis is recognized as a causative organism of the skin that may present as an abscess, ulcer, or granuloma with or without "sporotrichoid" spread, and rarely causes systemic disease⁴⁾. Kalb *et al.*⁵⁾ reported two cases caused by traumatic inoculation of *N. brasiliensis* from soil-contaminated material, and cutaneous involvement of nocardiosis may develop as one of four types: (a) mycetoma, (b) lymphocutaneous (sporotrichoid) infection including a cervicofacial variant in children, (c) superficial skin infection such as cellulitis, abscesses, ulcers, or granulomas, and (d) systemic disease with cutaneous involvement. Interestingly, they found over 80% of the patients with lymphocutaneous nocardiosis were male (hand or forearm) with a history of farm or garden work.

Our case appears to belong to a combined type of (a) and (b). Artificial occlusion due to skin-autograft after the traffic accident injury on the foot might have played an important role in the invasion of *Nocardia* elements into the subcutaneous tissue. However, there is a smaller possibility or suspicion of traumatic inoculation such as an insect bite or cat scratch as reported by O'Connor and Dire¹³⁾ and Sachs¹⁴⁾, although there was no

Table. Cutaneous nocardiosis due to *N. brasiliensis* in Japan

No.	Reporter	Year	Age	Sex	Clinical features	Trauma	Complication
1	Fukushiro <i>et al.</i> (17)	1955	38	F	mycetoma		
2	Yamada <i>et al.</i> (17)	1968	27	F	mycetoma		
3	Takizawa <i>et al.</i> (17)	1972	40	M	mycetoma	+	
4	Hironaga <i>et al.</i> (17)	1974	8	F	cutaneous lymphatic		
5	Yamamoto <i>et al.</i> (17)	1976	80	M	localized	+	
6	Yasuraoka <i>et al.</i> (17)	1980	69	F	localized	+	
7	Morino <i>et al.</i> (17)	1983	7	M	cutaneous lymphatic		
8	Hanawa <i>et al.</i> (17)	1984	44	M	mycetoma	+	
9	Nishimoto <i>et al.</i> (17)	1985	47	M	metastatic abscess	+	chronic myelocytic leukemia
10	Kobayashi <i>et al.</i> (17)	1985	69	M	cutaneous lymphatic	+	
11	Komatsu <i>et al.</i> (17)	1986	25	M	mycetoma	+	
12	Mori <i>et al.</i> (17)	1986	55	M	metastatic subc abscess		
13	Yoshinaga <i>et al.</i> (17)	1987	44	F	localized	+	
14	Harada <i>et al.</i> (17)	1987	80	M	cutaneous lymphatic	+	pemphigus foliaceus
15	Shiraki <i>et al.</i> (17)	1988	6	M	cutaneous lymphatic	+	
16	Nakashima <i>et al.</i> (17)	1988	58	M	systemic	+	nephrose
17	Murata <i>et al.</i> (17)	1988	69	F	mycetoma	+	aplastic anemia
18	Oonishi <i>et al.</i> (17)	1989	19	F	mycetoma	+	
19	Miyagawa <i>et al.</i> (17)	1989	45	M	localized	+	
20	Hironaga <i>et al.</i> (17)	1989	8	F	localized	+	
21	Sasaki <i>et al.</i> (17)	1990	87	M	cutaneous lymphatic	+	
22	Miyagawa <i>et al.</i> (17)	1991	45	M	localized	+	
23	Iimori <i>et al.</i> (17)	1991	53	F	lymphatic		
24	Yamura <i>et al.</i> (17)	1991	54	M	cutaneous lymphatic	+	
25	Kusuhara <i>et al.</i> (17)	1991	75	F	localized	+	
26	Yamura <i>et al.</i> (17)	1991	75	M	cutaneous lymphatic	+	
27	Tutiihashi <i>et al.</i> (17)	1992	82	M	localized	+	
28	Sasaki <i>et al.</i> (17)	1992	66	M	cutaneous lymphatic	+	
29	Ikedo <i>et al.</i> (18)	1993	7	M	localized	+	
30	Isonuma <i>et al.</i> (19)	1993	7	F	localized	+	
31	Yasui <i>et al.</i> (20)	1993	72	F	mycetoma	+	
32	Ryujin <i>et al.</i> (21)	1993	5	M	cutaneous lymphatic	+	asthma
33	Ryujin <i>et al.</i> (21)	1993	4	F	cutaneous lymphatic	+	asthma
34	Yoshida <i>et al.</i> (22)	1994	53	F	cutaneous lymphatic	+	SLE
35	Motizuki <i>et al.</i> (23)	1994	15	M	mycetoma	+	
36	Motizuki <i>et al.</i> (23)	1994	23	M	mycetoma	+	
37	Nishio <i>et al.</i> (24)	1994	31	F	mycetoma	+	
38	Nishio <i>et al.</i> (24)	1994	76	M	lymphatic	+	
39	Kimura <i>et al.</i> (25)	1994	68	M	lymphatic		
40	Naka <i>et al.</i> (26)	1995	84	M	cutaneous lymphatic	+	hypothyroidism
41	Asaka <i>et al.</i> (27)	1996	9	F	cutaneous lymphatic		
42	Ibe <i>et al.</i> (28)	1996	58	F	localized		
43	Kadono <i>et al.</i> (29)	1996	63	M	lymphatic		
44	Baba <i>et al.</i> (30)	1996	71	M	metastatic subc abscess		multiple polychondritis
45	Hayashida <i>et al.</i> (31)	1996	77	M	multiple subc abscess		lung nocardia
46	Ye <i>et al.</i> (7)	1997	82	M	cutaneous lymphatic	+	prostate cancer
47	Kubota M <i>et al.</i> (32)	1999	84	M	mycetoma	+	
48	Our case	2000	23	F	mycetoma & lymphatic	+	

clear evidence indicating this type of accidental inoculation.

It is especially of interest to note in this case that the lesion developed on the grafted skin on the dorsum of the foot more than 20 years after the graft. *N. brasiliensis* is well known to have a stronger virulence than *N. asteroides* as reported by Conde *et al.*¹⁵⁾ and Tsuboi *et al.*¹⁶⁾.

In addition, laboratory investigations revealed no abnormalities except leukocytosis, elevated blood

sedimentation rate and C-reactive protein with positive rheumatoid factor, so that immunodeficiency should not be associated in this occurrence.

There have been 49 reports of cutaneous nocardiosis due to *N. brasiliensis* including our case in Japan^{7, 17-31)}. Among the types of nocardiosis, nocardial mycetoma, localized and lymphocutaneous types of nocardiosis, lymphocutaneous types are predominant, especially in

older males and children; few examples have been seen among younger persons as in our case, however.

Treatment with trimethoprim/sulfamethoxazole is usually curative⁶⁾, however, total resection was needed in this case where the usual antibiotics were ineffective. Not only culture but also drug susceptibility should be determined for diagnosis and management of this disease, because oral administration of the antibiotic drugs, cephalosporin and ofloxacin were not curative in our case. We also learned that nocardiosis should be kept in mind when cutaneous infections do not respond to standard antibiotics as suggested by O'Connor and Dire¹³⁾.

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References

- 1) Boiron P, Locci R, Goodfellow M, Gumaa SA, Isik K, Kim B, McNeil MM, Salinas Carmona MC, Shojaei H: *Nocardia*, nocardiosis and mycetoma. *Med Mycol* **36** Suppl 1: 26-37, 1998.
- 2) Folgaresi M, Ferdani G, Coppini C, Pincelli C: Primary nocardiosis. *Eur J Dermatol* **8**: 430-431, 1998.
- 3) Akan H, Akova M, Ataoglu H, Aksu G, Arslan O, KoA H: *Rhodococcus equi* and *Nocardia brasiliensis* infection of the brain and liver in a patient with acute nonlymphoblastic leukemia. *Eur J Clin Microbiol Infect Dis* **17**: 737-739, 1998.
- 4) Bhalodia AM, Lertzman BH, Kantor GR, Granick MS: Localized cutaneous *Nocardia brasiliensis* mimicking foreign body granuloma. *Cutis* **61**: 161-163, 1998.
- 5) Kalb RE, Kaplan MH, Grossman ME: Cutaneous nocardiosis. Case reports and review. *J Am Acad Dermatol* **13**: 125-133, 1985.
- 6) Palmer SM Jr, Kanj SS, Davis RD, Tapson VF: A case of disseminated infection with *Nocardia brasiliensis* in a lung transplant recipient. *Transplantation* **63**: 1189-1190, 1997.
- 7) Ye Z, Shimomura H, Kudo S, Arao T, Sato Y, Ono T: A case of lymphocutaneous nocardiosis with a review of lymphocutaneous nocardiosis reported in Japan. *J Dermatol* **23**: 120-124, 1996.
- 8) Smego RA Jr, Gallis HA: The clinical spectrum of *Nocardia brasiliensis* infection in the United States. *Rev Infect Dis* **6**: 164-180, 1984.
- 9) Callen JP, Kingman J: Disseminated cutaneous *Nocardia brasiliensis* infection. *Pediatr Dermatol* **2**: 49-51, 1984.
- 10) Moeller CA, Burton CS III: Primary lymphocutaneous *Nocardia brasiliensis* infection. *Arch Dermatol* **122**: 246-247, 1986.
- 11) Zecler E, Gilboa Y, Elkina L, Atlan G, Sompolsky D: Lymphocutaneous nocardiosis due to *Nocardia brasiliensis*. *Arch Dermatol* **113**: 642-643, 1977.
- 12) Bates RR, Rifkind D: *Nocardia brasiliensis* lymphocutaneous syndrome. *Am J Dis Child* **121**: 246-247, 1971.
- 13) O'Connor PT, Dire DJ: Cutaneous nocardiosis associated with insect bites. *Cutis* **50**: 301-302, 1992.
- 14) Sachs MK: Lymphocutaneous *Nocardia brasiliensis* infection acquired from a cat scratch: case report and review. *Clin Infect Dis* **15**: 710-711, 1992.
- 15) Conde C, Melendro EI, Fresan M, Ortiz LO: *Nocardia brasiliensis*: Mycetoma induction and growth cycle. *Infect Immun* **38**: 1291-1295, 1982.
- 16) Tsuboi R, Takamori K, Ogawa H, Mikami Y, Arai T: Lymphocutaneous nocardiosis caused by *Nocardia asteroides*. Case report and literature review. *Arch Dermatol* **122**: 1183-1185, 1986.
- 17) Takahashi Y, Ooida M, Hayakawa H, Nakajima H: Rare but typical cutaneous mycosis. 37th Jpn Mycol Meeting Committee ed. pp211-216, Zuiho Publish, Tokyo, 1994 (in Japanese).
- 18) Ikeda N, Hiramatsu M, Kobayashi T, Miki T, Suzuki A, Takasaki Y, Kawamitsu T, Yamakura S, Hyakui T: A case of cutaneous nocardiosis due to *Nocardia brasiliensis*. *Med J Wakayama Red Cross Hosp* **11**: 137-140, 1993 (in Japanese).
- 19) Isonuma H: Chemotherapy for the management of nocardiosis-susceptibility of *Nocardia* species isolated from 6 clinical cases of nocardiosis. *Juntendo Med J* **38**: 552-556, 1993 (in Japanese).
- 20) Yasui K, Ikeda M, Yamamoto Y, Kodama H: A case of actinomycetoma. *Jpn J Med Mycol* **34** (Suppl.): 173, 1993 (in Japanese).
- 21) Ryujin A, Yagi H, Oku T, Usami H, Nishiyama N: Lymphocutaneous nocardiosis involving children. *Hifubyoh-shinryoh* **15**: 779-782, 1993 (in Japanese).
- 22) Yoshida M, Sugiyama Y, Harada M, Tezuka T, Iimori M, Hiruma M: Lymphocutaneous nocardiosis with multiple subcutaneous nodules distributed over the extensor aspect of the forearm. Report of a case. *Acta Dermatovenereol* **74**: 447-448, 1994.
- 23) Mochizuki T, Omoto M, Tanaka S, Watanabe S, Uehara M, Hayashi S, Miyauchi T, Mikami Y: Two cases of primary cutaneous nocardiosis caused by *Nocardia brasiliensis*. *Hifukakiyou* **89**: 491-497, 1994 (in Japanese).
- 24) Nishio T, Sasai Y, Matsumoto J, Kaji H, Nagata M: Two cases of cutaneous nocardiosis caused by *Nocardia brasiliensis*. *Jpn J Clin Dermatol* **48**: 37-41, 1994.
- 25) Kimura K, Kuyama M, Mitsugi M: Cutaneous nocardiosis of the face. *Rinsho Derma(Tokyo)* **36**: 1532-1533, 1994 (in Japanese).
- 26) Naka W, Miyakawa S, Niizeki H, Fukuda T, Mikami Y: Unusually located lymphocutaneous nocardiosis caused by *Nocardia brasiliensis*. *Br J Dermatol* **132**: 609-613, 1995.
- 27) Asaka T, Fukushima R, Watanabe K, Koshida R, Kitamura K: A child case of cutaneous

- nocardiosis caused by *Nocardia brasiliensis*. Igakukensa **45**: 1360-1363, 1996 (in Japanese).
- 28) Ibe H, Harada M, Katai A, Tanaka T, Wada K, Sakamoto T: A case of cutaneous nocardiosis in the mental region. Jpn J Oral Surg **42**: 614-616, 1996 (in Japanese).
- 29) Kadono T, Kajima M, Nakabayasi K: Cutaneous nocardiosis on the face. Rinsho Derma (Tokyo) **38**: 1837-1839, 1996 (in Japanese).
- 30) Baba Y, Inoue Y, Tajima K, Fukushiro R, Ikeda S, Ishikawa K: Metastatic subcutaneous abscess caused by *Nocardia brasiliensis*. Nishinohon J Derm **57**: 1003-1008, 1995 (in Japanese).
- 31) Hayashida S, Yamamoto K, Shiraishi Y, Satho S, Ishida K: A case of cutaneous nocardiosis caused by *N. brasiliensis* followed by pulmonary nocardiosis. J Jpn Ass Rural Med **45**: 351, 1996 (in Japanese).
- 32) Kubota M, Hirai K, Sakabira I, Ishida H, Ishiguro K, Kumakiri M, Yada S, Kimura N, Mikami Y: A case of cutaneous localized nocardiosis with effect by local warming therapy. Rinsho Derma (Tokyo) **41**: 1353-1357, 1999 (in Japanese).