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Case and Review

Cutaneous Nocardiosis Simulating Cutaneous Lymphatic Sporotrichosis

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Keywords
Nocardiosis · Sporotrichosis · Subcutaneous mycosis · Sporothrix · *Nocardia brasiliensis*

Abstract
Sporotrichosis is the subcutaneous mycosis caused by several species of the Sporothrix genus. With worldwide occurrence, the State of Rio de Janeiro is presently undergoing a zoonotic sporotrichosis epidemic. The form of lymphocutaneous nocardiosis is rare, being caused especially by *Nocardia brasiliensis*. It appears as a nodular or ulcerated lesion, with multiple painful erythematous nodules or satellite pustules distributed along the lymphatic tract, similar to the lymphocutaneous variant of sporotrichosis. We present a 61-year-old man who, after an insect bite in the left leg, developed an ulcerated lesion associated with ascending lymphangitis, nonresponsive to previous antibiotic therapies. The patient was admitted for investigation, based on the main diagnostic hypothesis of lymphatic cutaneous sporotrichosis entailed by the highly suggestive morphology, associated with the epidemiologic information that he is a resident of the city of Rio de Janeiro. While culture results were being awaited, the patient was medicated with sulfamethoxazole-trimethoprim to cover CA-MRSA and evolved with total healing of the lesions. After hospital discharge, using an ulcer

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fragment, an *Actinomyces* sp. was cultivated and *N. brasiliensis* was identified by molecular biology. The objective of this report is to demonstrate a case of lymphocutaneous nocardiosis caused by *N. brasiliensis* after a probable insect bite. Despite the patient being a resident of the State of Rio de Janeiro (endemic region for sporotrichosis), it is highlighted that it is necessary to be aware of the differential diagnoses of an ulcerated lesion with lymphangitis, favoring an early diagnosis and appropriate treatment of the illness.

Introduction

Sporotrichosis is a subcutaneous mycosis caused by different species of the genus *Sporothrix* [1]. With worldwide occurrence, it is common in Latin America [1]. It was already reported in Brazil in 1907 by Lutz and Splendore [2]. The State of Rio de Janeiro is presently undergoing a zoonotic epidemic with onset in 1997 [3, 4]. The infection is usually acquired by inoculation of the fungus into the skin. *Sporothrix* spp. generally live in decaying organic matter, and therefore activities involving soil and handling contaminated vegetation become favorable for contamination [1, 3]. An alternative transmission way is through infected animals, mainly cats, considered as an important risk factor to acquire the mycosis [1, 3–5]. The most frequent clinical form of sporotrichosis in humans is the lymphocutaneous form, with nodules along the lymphatic vessels that can cause ulceration [1, 3].

Nocardiosis, at its turn, is a rare opportunistic disease potentially fatal, caused by several species of the genus *Nocardia* (family: *Nocardiaceae*; order: *Actinomycetales*) [6–9]. The infection can be systemic or cutaneous [7, 8, 10]. Systemic nocardiosis is more common, especially in immunocompromised patients. It is frequently caused by *Nocardia asteroides*, which affects almost exclusively the respiratory tract caused by inhalation of the pathogen [6, 8, 10]. Cutaneous nocardiosis features several clinical manifestations, which can be divided into three forms: (1) actinomycetoma, (2) superficial skin infection (pustules, abscess, pyoderma, granulomas, or cellulitis), and (3) lymphocutaneous [6, 8, 11]. Some authors also suggest secondary infection caused by the hematogenous dissemination as a fourth cutaneous form.

The lymphocutaneous form of nocardiosis is mainly caused by *Nocardia brasiliensis* [8, 9, 11]. Lower limbs are most commonly affected, followed by hands, especially in patients with a history of trauma during gardening activities [6, 8, 9, 11–14]. Clinically, it appears as a nodular or ulcerated lesion, with painful multiple erythematous nodules or satellite pustules distributed along the lymphatic tract [6, 11]. This presentation is similar to the lymphocutaneous form of sporotrichosis, being often called sporotrichoid by some authors [6–9, 11, 15, 16].

Case Report

A 61-year-old married man, retired administrative agent, and resident in Campo Grande, Rio de Janeiro was referred with fever, ulceration, and lymphangitis beginning a week after an insect bite in the left leg. After seeking medical help, he received a prescription of third-generation cephalosporin. In view of lack of improvement, the patient went to our University Hospital, where he was admitted for investigation and treated for pyoderma with 1 g cephalexin, administered orally every 6 h.

Due to the persistence of the clinical picture, a consultation by our Sector of Dermatology was requested. At the occasion, the patient had a single ulcerated lesion with infiltrated borders, approximately 2 cm in diameter, located in the lateral malleolar region (Fig. 1), associated with the erythematous lymphatic cord with some subcutaneous nodules in its pathway, extending from the ulcer to the proximal thigh region (Fig. 2). The patient also presented left inguinal lymph node enlargement of approximately 1.5 cm in diameter with phlogistic signs. No lesions in the remainder of the tegument were found. At that point, the diagnostic hypothesis of lymphocutaneous sporotrichosis was considered, with the following differential diagnoses: American tegumentary leishmaniasis and atypical mycobacteriosis. A biopsy of the ulcerated lesion was performed and forwarded for histopathological, mycological, and mycobacteriological studies.

Leukocytosis of 19,600/mm^3 with monocytosis, PCR of 115.4 mg/L, and negative anti-HIV were some of the results from the lab analyses. Nose swab was negative and cytopathology with ulcer imprint did not show amastigote form in the ulcer base. An acute and chronic inflammatory process with ulceration was found by histopathological examination, while direct mycological examination was negative.

After a week in the hospital, the patient still had fever, leukocytosis, and little improvement of the ulcerated lesion in addition to nodule suppuration in the lymph cord. Aiming to expand the antibiotic spectrum to cover CA-MRSA, intravenous sulfamethoxazole-trimethoprim (400 mg + 80 mg) was applied intravenously with 4 vials every 12 h.

Starting on the third day of the new treatment, the patient presented an important therapeutic response, without fever and progressive improvement of the ulcer. After 9 days of treatment, he was sent home with the recommendation to continue cephalexin and sulfamethoxazole-trimethoprim until completing 14 days.

After the patient's discharge from the hospital, the mycological culture of the biopsied fragment in Sabouraud agar medium demonstrated growth of *Actinomyces* sp. (Fig. 3, Fig. 4).

The isolated fungus was forwarded to the Collection of Bacteria from Environment and Health of the Oswaldo Cruz Foundation in Rio de Janeiro, where molecular studies to identify the species of actinomycetes were performed. In order to expand the genus, 16S rRNA, polymerase chain reaction (PCR) was carried out using the universal initiators PA (5′-3′AGAGTTTGATCCTGGCTCAG) and PH (5′-3′AAGGAGGTGATCCAGCCGCA). The PCR product was purified and utilized as DNA mold for the sequencing reaction applying the commercial BigDye Terminator (Cycle Sequencing Ready Reaction Kit). After running the sequencer (ABI PRISM 3730 Applied Biosystems DNA Sequencer), the nucleotide sequences were analyzed and edited using the SeqMan version 7.0 (DNASTAR Lasergene) program and compared to those deposited in the sequences database: GenBank (http://www.ncbi.nlm.nih.gov/) and EzTaxon (http://www.ezbiocloud.net/eztaxon). In consequence, the species *N. brasiliensis* (CBAS 585/B518/2015) was identified.

The patient was summoned back to the hospital for reassessment and proposition for treatment extension; however, the patient refused, claiming understanding that the cutaneous lesion had already been cured (Fig. 5).

Discussion

This is the report of a case of a healthy man with lymphocutaneous presentation of nocardiosis acquired possibly after an insect bite. *Nocardia* spp. dwell in the soil, leading to suppose that, in some way, the insect bite represented an access door to the pathogen, either

through the vector or by contamination of the open wound [6, 8]. In the consulted medical literature, only two cases of lymphocutaneous nocardiosis by *N. brasiliensis* were found after an insect bite. In 1992, a 26-year-old male patient was reported having been bitten by an insect in the left lower limb while camping outdoors. Later, a pustular lesion with lymphangitis and inguinal adenomegaly appeared. The patient was treated satisfactorily with amikacin and sulfamethoxazole-trimethoprim [17].

Paredes et al. [8] also reported a 56-year-old male patient who presented an ulcer with hemorrhagic center in the right calf, painful nodular lymphangitis, and fever after an insect bite. This patient was treated with sulfamethoxazole-trimethoprim, followed by minocycline due to allergy.

Cutaneous nocardiosis has a preference to affect men with ages between 21 and 50 years [6–8, 11, 12, 14]. This fact could be explained by the higher occupational exposure of men to such pathogen [6, 11, 12].

The lymphocutaneous form of nocardiosis is uncommon, representing about 20–25% of cutaneous nocardioses. Sporotrichosis is its main differential diagnosis [9, 15]. The reported patient is a resident of the State of Rio de Janeiro, where the incidence of sporotrichosis cases has been increasing in the last 19 years, exceeding 5,000 cases, as recorded in the Evandro Chagas National Institute of Infectious Diseases (reference unit in Rio de Janeiro) [3]. The morphotopography of the lesion in association with the epidemiological history suggested the hypothesis of sporotrichosis; however, it must be considered that the clinical presentation of a nodule-ulcerated lesion with lymphangitis encompasses other differential diagnoses, such as bacterial pyoderma, atypical mycobacteriosis, histoplasmosis, cryptococcosis, blastomycosis, paracoccidioidomycosis, coccidioidomycosis, and chromoblastomycosis, among others [6, 8–11, 15, 16].

Paredes et al. [8] and Dodiuk-Gad et al. [18] recommend some criteria for diagnostic investigation of primary cutaneous nocardiosis: outdoor lesion history or insect bites (farmer, gardener), cutaneous infections that do not respond to usual antibiotics, presence of cutaneous lymphangitis with intense erythema and fever, recurrences, chronic or post-traumatic suppurative lesion, and slow culture growth. A detailed diagnostic investigation averts a late diagnosis of the disease.

Another great difficulty is the correct identification of *Nocardia* spp. The histological findings merely suggest an unspecific infectious process; at culture, the microorganism can usually only be visualized when Gram stain is used. Additionally, it is a slow-growing bacteria (between 2–3 weeks), suggesting that the lab must be on alert whenever a suspicion of nocardiosis arises [6–19]. Contrary to actinomycetes, *Sporothrix* spp. grows very fast in mycological culture, usually within 5–10 days.

The treatment of choice for nocardiosis is sulfamethoxazole-trimethoprim [6, 8, 10, 11, 19]. No consensus exists regarding treatment periods, varying between 2–4 months, which may be extended to prevent recurrence [6–8, 15–17]. Other alternatives would be amikacin, third generation cephalosporins, minocycline, imipenem, and linezolid [6–8, 10–12]. It is worth to point out that, in the case described, as well as in other reports in the literature [9, 15, 20, 21], the patients did not show an immediate improvement when medicated previously with other antibiotics due to lack of correct identification of *Nocardiosis* spp.

Conclusion

A case of lymphocutaneous nocardiosis caused by *N. brasiliensis* was reported after a probable insect bite. Despite the patient being a resident of the State of Rio de Janeiro (endemic region for sporotrichosis), it is highlighted that it is necessary to be aware of the differential diagnoses of an ulcerated lesion with ascending lymphangitis, favoring an early diagnosis and appropriate treatment of the illness.

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Statement of Ethics

The authors have no ethical conflicts of interest to disclose.

Disclosure Statement

The authors have no conflict of interest for this article.

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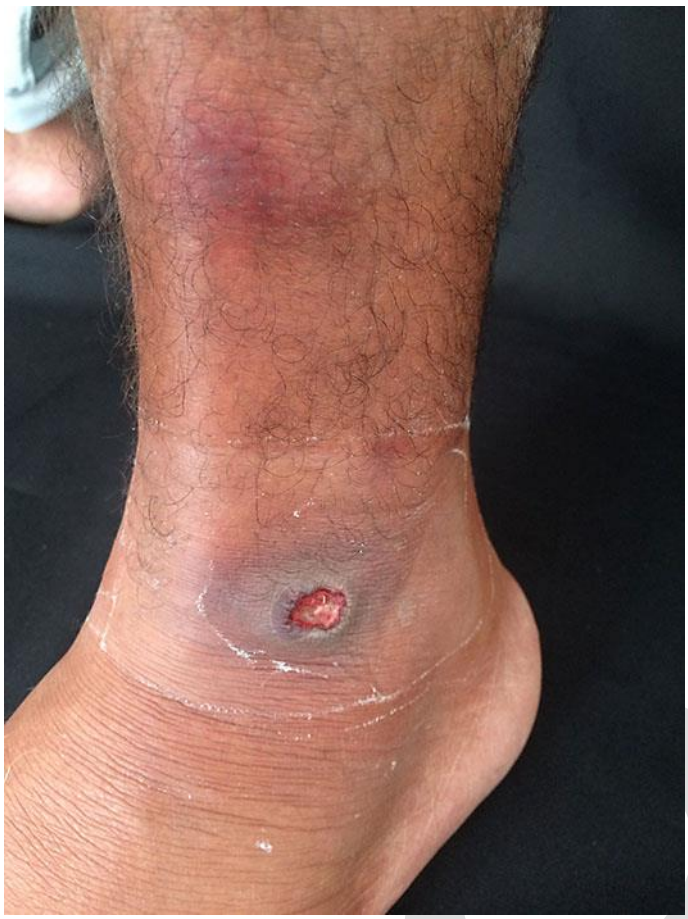

Fig. 1. Ulcerated lesion at the left lateral malleolus.

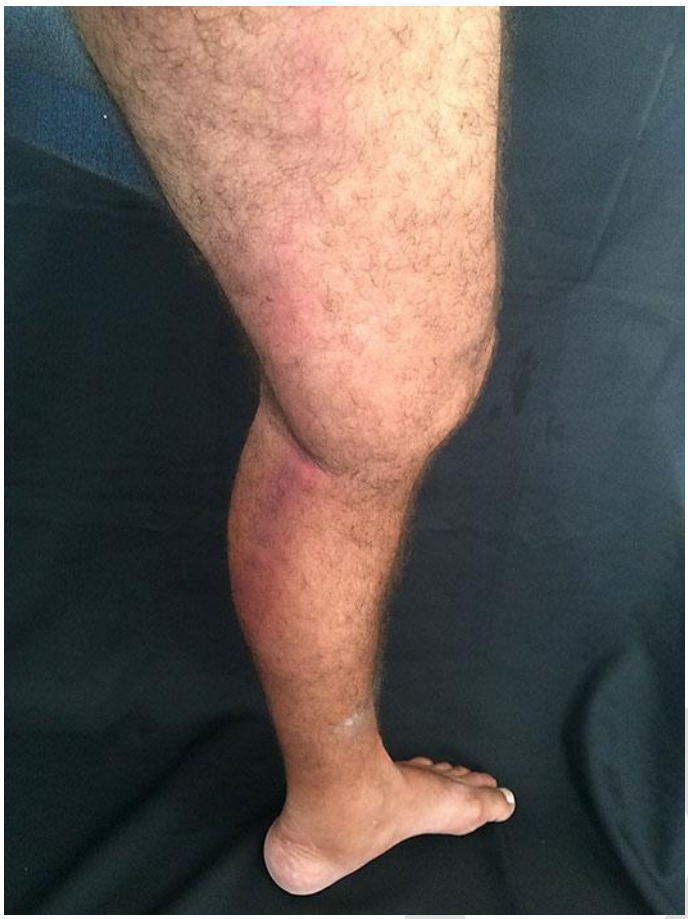

Fig. 2. Ascending lymphangitis in the left lower limb.

Fig. 3. *Nocardia brasiliensis* colony in Sabouraud agar medium.

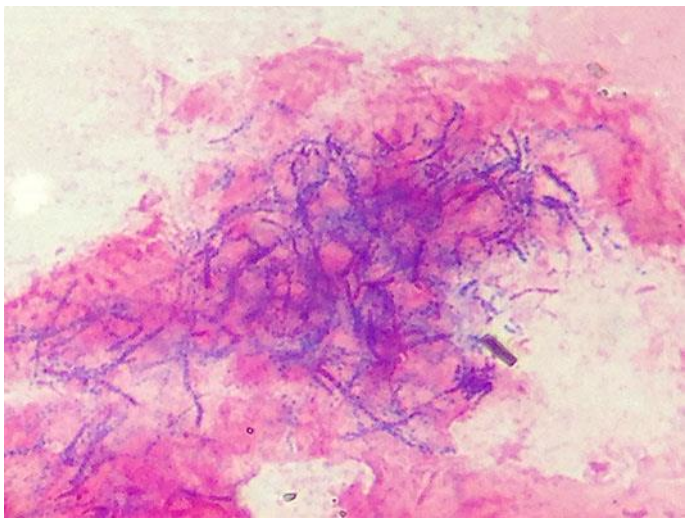

Fig. 4. Gram-positive thin and branched bacterial filaments (Gram, ×1,000).

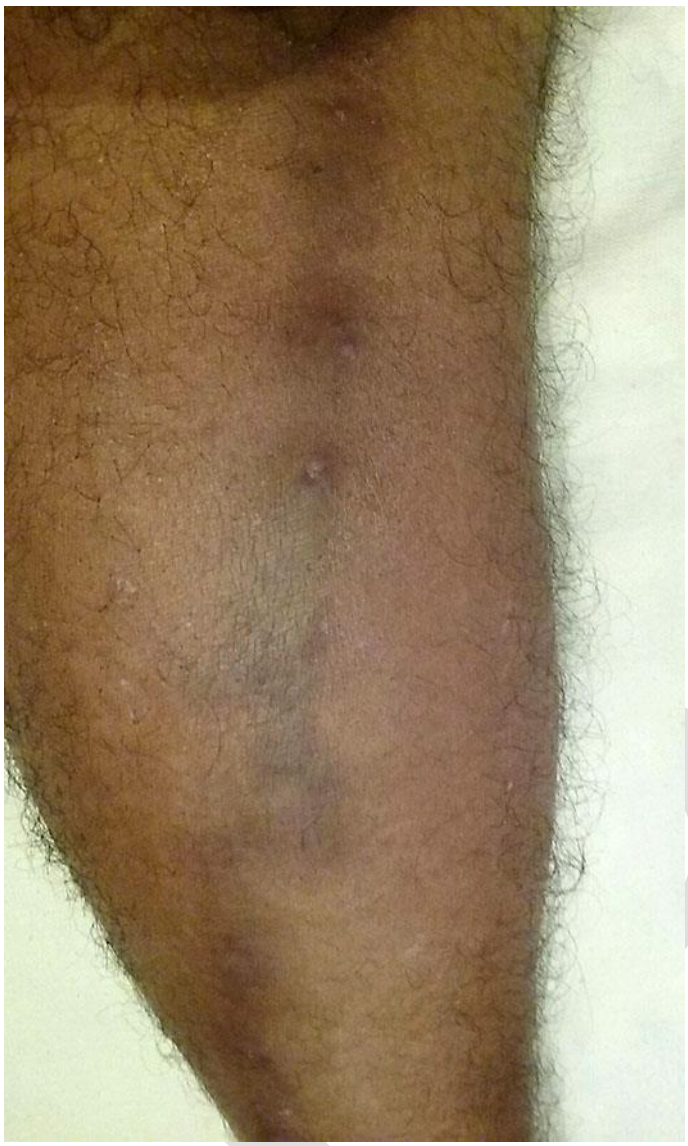

Fig. 5. Hyperchromic cicatricial macule following the lymphatic cord.