

# Cutaneous nocardiosis and its various presentations

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## ABSTRACT

Cutaneous nocardiosis is a rare opportunistic infection found in both immunocompromised and immunocompetent patients. We describe three male immunocompromised patients who exhibited different clinical forms of cutaneous nocardiosis. All of them were under corticosteroid treatment (Dermatol Argent 2010;16(3):195-198).

## Keywords:

*cutaneous nocardiosis, immunosuppression, corticosteroid.*

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## Introduction

Cutaneous nocardiosis is a rare entity which usually occurs in immunocompromised patients.<sup>1,2</sup> It is classified into four clinical forms: a) superficial, b) lymphocutaneous, c) disseminated disease with secondary commitment of skin and d) mycetoma.<sup>2,3-6</sup> Diagnosis is usually delayed, because different morphological aspects cause confusion and pose differential diagnosis on pyoderma, sporotrichosis, or fungal infections.<sup>1</sup> In this work, three patients with different clinical forms of cutaneous nocardiosis are described.

## Case 1

Male patient aged 32, a rural worker native of the province of Santa Fe. Presents a history of liver transplant due to a secondary biliary cirrhosis, under treatment with methylprednisolone 40 mg/day and tacrolimus 14 mg/day. He is hospitalized with a 3×2 cm oval ulcer, with painful serohematic and necrotic background material. Associated to this injury, he presented four erythematous nodules, hot, fluctuant and painful on palpation, induration of underlying lymphatic cord (**Photo 1**), and painful ipsilateral inguinal lymphadenopathy. Bacteriological and mycological cultures revealed coinfection with *Exophiala jaenselmei* and *Nocardia brasiliensis*. Treatment was initiated with itraconazole 600 mg/day, trimethoprim 320 mg/day and sulfamethoxazole 1600 mg/day (TMP-SMX) with complete recovery from the lesions within 4 months of treatment.

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**PHOTO 1.** Oval ulcer and erythematous nodules following the lymphatic path.



**PHOTO 2.** Violaceous inflammatory tumor with multiple mouths emanating purulent discharge, on outer right ankle.

## Case 2

Male patient aged 43, a rural worker native of the province of Formosa. He is admitted in our institution with a paraneoplastic Cushing syndrome secondary to a neuroendocrine tumor. Physical examination showed a painful violaceous tumor of 6×3 cm with an eroded surface on the external face

of the right ankle. The lesion had fistulas draining purulent material containing granules of yellow/white color (**Photo 2**). The lesion appeared after local trauma, a month before his hospitalization. *Nocardia spp* was isolated from a culture of material obtained by needle aspiration using a Lowenstein-Jensen media. The patient was treated with TMP-SMX 320-1600 mg/day during six months, with partial improvement. The patient died of secondary complications to his cancer treatment.

## Case 3

83 year old male patient with a history of hemolytic anemia treated with meprednisona 60 mg/day. At the time of admission the patient was febrile and had erythematous-violaceous rounded nodules, of 2 cm in diameter, slightly indurated, painful, and located in the left thigh, abdomen and right arm (**Photo 3**). Axial computed tomography of the chest revealed a consolidation in the lower left lung lobe. MRI of the central nervous system showed a nodular lesion in the right region of the frontal lobe, with a peripheral highlight after intravenous administration of gadolinium. *Nocardia spp.* was isolated from the skin culture using Lowenstein-Jensen media. Intravenous treatment with TMP-SMX was initiated administrating 15 and 75 mg/kg/day respectively during two weeks, and then continued orally with 320 mg of trimethoprim and 1600 mg of sulfamethoxazole per day during 6 months with complete healing of lesions.

## Comments

The *Nocardia* type belongs to the family *Nocardiaceae*, from the order *Actinomycetales*. The predominant pathogenic species in humans are complex *N. asteroides*, *N. brasiliensis* and *N. oititidiscaviarum*.<sup>7-9</sup> The species most commonly affecting the skin is *N. brasiliensis*.<sup>8</sup>

This infection affects more men than women (3:1) and its incidence is highest between 30 and 50 years of age. The natural habitat of the pathogen is soil, particularly the one that contains the remains of vegetables and decaying material.<sup>3,7</sup> The geographic distribution of *Nocardia* is universal. In our country is frequently observed in the wild-tucuman jungles or Yungas (Tucumán, Jujuy and Salta), where one of the characteristic clinical forms is observed, the mycetoma, typical of rural workers.<sup>1,10-12</sup>

Nocardiosis is most common in immunocompromised individuals. The most important defense mechanisms against these infection are polymorphonuclear cells (PMN) and cell-mediated immunity.<sup>7</sup> Risk factors for infection include immunosuppressive therapy (in particular corticosteroids), neoplastic diseases and transplantation (after the first 6 months).<sup>13,14</sup> Predisposing factors not related to immunosuppressive states include traumatic inoculation during surgery, exposure to contaminated materials and to ongoing trauma, and intravenous drug abuse.<sup>3</sup>

There are four ways in which the cutaneous nocardiosis can present itself.

- *Superficial infection*, clinically indistinguishable from lesions caused by pyogenic bacteria may present itself as abscesses, cellulitis, chronic ulcers, nodules of slow growth or pustules. The most common location is on the limbs.<sup>1,3,9</sup>
- *Lymphocutaneous syndrome* is characterized by an ulcerated nodule or papule on the site of traumatic inoculation, followed by ascending lymphangitis and the presence of erythematous nodules along the path of lymphatic vessels that drain the area. This form accounts for 20 to 25% of cases of nocardial skin infection.<sup>8</sup> The most frequent location is on the face and the limbs.<sup>5</sup>
- *Systemic or disseminated infection* is diagnosed when two or more organs are infected. The sites most often affected are the CNS, skin, eyes (especially the retina) and kidneys.<sup>9</sup> Cutaneous involvement is present in 2% of cases. The lesions may appear as pustules, abscesses or nodules of soft consistency that sometimes ulcerate and drain a purulent material.<sup>16,17</sup>
- *Mycetoma* is a hard and painful inflammatory tumor, which is accompanied by progressive deformation of the affected area and draining fistulae which exudate granules usually of a yellowish-white color.<sup>18</sup> It may extend into subcutaneous tissue and compromise the adjacent muscle and bone, leading to a destructive osteomyelitis.<sup>9</sup> The most commonly affected sites are the lower limbs, especially feet.<sup>11,12</sup>

Diagnosis is based on microscopic observations and cultures. Under direct microscopic examination, nocardia is presented as a filamentous bacteria, branched, acid-resistant, Gram and Kinyoun positive (**Photo 4**).<sup>3,9</sup> The culture isolation can be difficult due to its slow growth, the ease with which it is obscured by the rapid development of other matching bacterial species, and also due to the antibiotics present in the culture media against fungi.<sup>3</sup> It is important to carry out the characterization of the species involved in the infection, because some are particularly resistant to antibiotics, such as *N. otitidiscaviarum*, which has different sensitivities to sulfonamides drugs.<sup>9,19</sup>

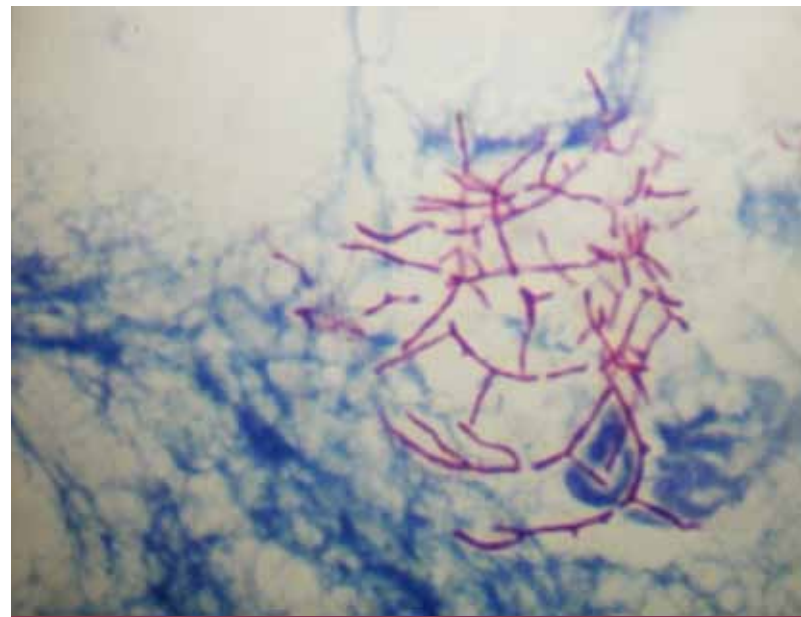
Anatomopathologic study of skin lesions contributes to the diagnosis, but is not definitive. It shows a dense polymorphonuclear infiltrate at dermal level, granulated tissue, fibrosis and granuloma formation (**Photo 5**).<sup>3</sup> Staining with hematoxylin eosine (HE) can show kidney-jarring grains with a basophilic center, surrounded by an eosinophilic hyaline strip "in sunshine" (Splendori-Hoppli phenomenon), forming sulfur granules.<sup>18</sup>

The treatment of choice for nocardiosis are sulfonamides. There are no official treatment guidelines, corroborated by controlled clinical studies.<sup>9,19</sup>

The most commonly used sulfonamide is the combination of trimethoprim-sulfamethoxazole (TMP-SMX), which is

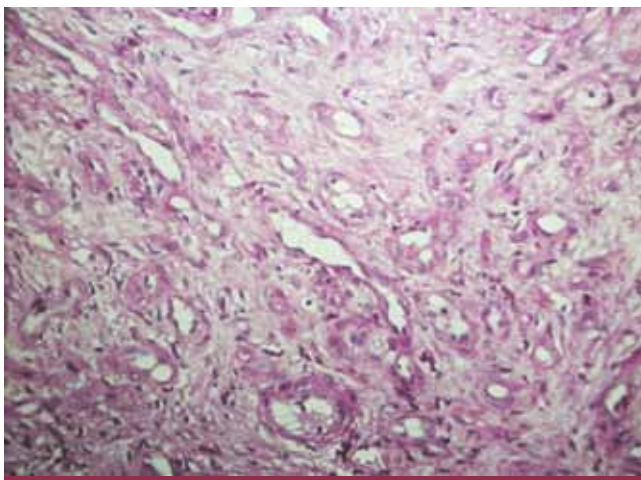


**PHOTO 3.** Softened erythematous nodule on upper limb.



**PHOTO 4.** Filamentous branching bacteria, Gram and Kinyoun positive on direct examination..

sold at a fixed ratio of 1:5. The recommended dose for localized nocardiosis is from 5 to 10 mg/kg/day of TMP and 25 to 50 mg/kg/day of SMX. In the event of widespread disease or brain abscess higher initial doses are recommended administered intravenously or orally.<sup>19</sup> As an alternative to sulfonamide drugs, there is some experience of treatment with amikacin, imipenem, third generation cephalosporins, minocycline and amoxicillin-clavulanic acid in normal used doses. The latter is particularly useful for the treatment of infections caused by *N. brasiliensis*, microorganism that



**PHOTO 5.** Little inflammatory infiltrate with granulated tissue (HE, 10X).

can be a producer of  $\beta$ -lactamases.<sup>19</sup> The uncomplicated primary cutaneous nocardiosis can be cured with an appropriate treatment of one to three months. The therapy of disseminated disease, usually, may require a period of twelve months and, sometimes, the combination of two drugs at the beginning of treatment.<sup>3,9,19</sup> Primary skin disease in patients without immunological disorders is usually of good prognosis. Disseminated disease is of a reserved prognosis and has a mortality rate of 7 to 44% in immunocompetent patients and more than 85% in immunocompromised patients.<sup>20,21</sup>

## Conclusion

Cutaneous nocardiosis is a rare infectious skin disease. Note that in all three discussed cases there is as a common predisposing factor, the presence of high serum levels of corticosteroids, either as a result of therapeutic intervention or secretion of an endogenous tumor.

In our patients we could see two types, Lymphocutaneous (case study 1) and mycetoma (clinical case 2) with its typical location in two young individuals dedicated to rural jobs, and a disseminated disease with secondary skin commitment (ase report 3) in an elderly patient, from the city area and immunocompromised. It is important to note that in all cases with cutaneous manifestations, possible CNS and lung involvement should always be investigated.

Given the difficulty of the organism to grow in culture media, it is important to alert the laboratory of the a clinical suspicion of this infection, so that material is processed properly. In our case we used the Löwenstein-Jensen media for the isolation of this bacterium, allowing adequate bacteriological rescue, early diagnosis and correct treatment in time.

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