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Uncommon lymphocutaneous cellulitis after insect bite: a case report of primary cutaneous nocardiosis and literature review

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SUMMARY

Nocardia is a genus of aerobic actinomycetes that are usually responsible for opportunistic infection in immunocompromised patients. Less frequently nocardiosis can interest immunocompetent population, causing especially primary cutaneous infections. Cutaneous involvement by *Nocardia* spp. may occur mostly as one of four clinical manifestations: superficial cellulitis or abscess, mycetoma, lymphocutaneous (also defined "sporotrichoid") infection and secondary cutaneous involvement from systemic disease. Infections usually present after minor local injury, especially in traumatic outdoor activities (*e.g.* gardeners, farmers, road accidents), with subsequent environmental contamination of the wound. In sporadic cases cutaneous infection follows an insect bite. Microbiological diagnosis is often difficult to obtain and *N. brasiliensis* is the species isolated in most cases (80%). We present the case of a 45-year-old female with fever and a painful and necrotizing lesion on her right leg with secondary ascending lesions occurred on the homolateral knee and consensual groin lymphadenopathy after insect sting (maybe a spider bite). Cultures on skin biopsy identified *Nocardia brasiliensis*. Infection was completely healed after 5 months of targeted antibiotic therapy. In addition, we performed a literature review of all cutaneous nocardiosis cases in immunocompetent individuals, finding that only in 22 cases the infection presented after insect bite; in most of these cases lymphocutaneous manifestation was seen and *N. brasiliensis* was the *Nocardia* species isolated. Our case, along with others in literature, reveals that the real burden of soft-tissues nocardiosis seems low but probably many cases might go undiagnosed because of difficulties in microbiology diagnosis. Primary cutaneous nocardiosis should be included in the diagnostic pathway in cases of cellulitis following insect bite or sting, especially when localized to extremities.

Keywords: nocardia, cutaneous nocardiosis, actinomycetes, insect bite, immunocompetent.

INTRODUCTION

Nocardia is a genus of aerobic actinomycetes which turns out to be a weakly Gram-positive and acid-fast bacterium. Unlike other Gram-positive bacteria, *Nocardia* spp. appear as filamentous bacteria with hyphae-like branching on direct microscopy [1]. *Nocardia* is usually an opportunistic pathogen and most infections occur in immunocompromised patients. In particular, patients with depressed cell-mediated immunity (*e.g.* HIV/AIDS, solid-organ transplanted patients, etc.) have a higher risk of nocardiosis. However, up to one-third of patients with nocardiosis are immunocompetent [1]. Clinical manifestations of nocardiosis include pulmonary disease, central nervous system (CNS) infections, systemic

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and primary cutaneous nocardiosis. Unlike other forms of nocardiosis, primary cutaneous nocardiosis develops more commonly in immunocompetent patients. Cutaneous involvement by *Nocardia* spp. may occur as several clinical manifestations: more frequently superficial cellulitis or abscess, mycetoma, lymphocutaneous (also defined "sporotrichoid") infection and secondary cutaneous involvement from systemic disease are seen [2]. However, presentation as pustules or nodules, granulomas, ulcerative, necrotic or keloid-like lesions and other non-specific cutaneous clinical lesion can be seen.

CASE PRESENTATION

We present the case of a 45-year-old female who presented to the emergency department complaining for fever and a painful and purplish lesion surrounded by erythema on her right leg. The patient reported an insect sting (maybe a spider bite) on her right leg while she was working in her garden three days prior to the admission. Her past medical history included oophorectomy for a previous ovarian cancer and *Helicobacter pylori*-related gastritis.

On clinical examination, she was febrile (max 38.6°C) and there was a black-purplish lesion surrounded by an erythematous halo on the right leg at the site of the insect bite (Figure 1, a), associated with cutaneous erythema. This necrotizing lesion showed in 48 hours a central ulcerative evolution and the erythematous halo expanded towards the periphery (Figure 1, b). Within the following 3 days, secondary ascending lesions occurred with swelling erythema of the homolateral knee and groin lymphadenopathy (Figure 1, c). Laboratory examinations showed increased values of C-reactive protein (25 mg/L, normal value <5 mg/L) and white blood cell count ($14x10^3/mm^3$).

The patient was then admitted to the Infectious Diseases Unit. In the meantime, a primary diagnosis of cellulitis was made, and intravenous therapy with amoxicillin/clavulanate (2.2 g intravenously every 6 hours) and clindamycin (900 mg intravenously every 8 hours) were commenced. Blood cultures yielded negative results. Since no improvement was observed, after 48 hours doxycycline (100 mg every 12 hours) was added to the regimen for empirical clindamycin-resistant *S. aureus* coverage. Clindamycin was continued for its anti-toxin effect. Despite antibiotic therapy, the patient remained feverish, the erythema continued to spread, and the black-purplish lesion kept expanding and necrotizing; C-reactive protein increased up to 160 mg/L. A computed tomography (CT)-scan of the leg showed images consistent with fasciitis of lateral face of thigh and leg, subcutaneous tissues swelling, and consensual enlarging inguinal lymphadenopathy.

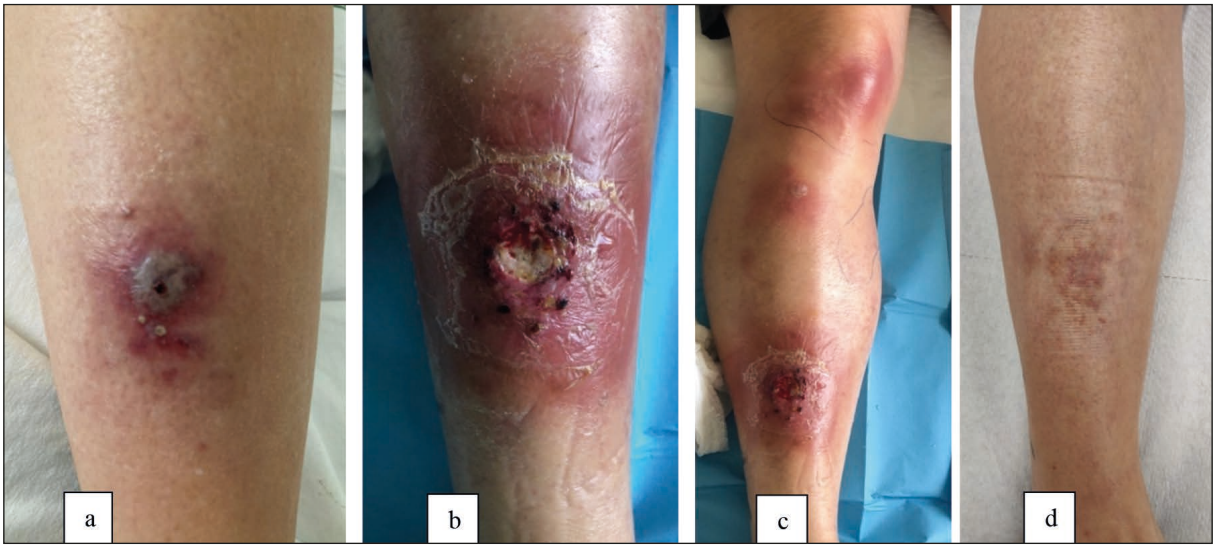

Figure 1 - Evolution of the tibial lesion at site of the insect bite (a, b); secondary ascending lesions (c) and outcome after treatment (d).

Samples for microbiological examination were collected by lesion biopsy. After 7 days of empirical therapy, culture turned out positive for weakly Gram-positive and acid-fast actinomycetes, identified as *Nocardia brasiliensis*. Susceptibility tests (CLSI breakpoints) showed resistance to ciprofloxacin (MIC 4), clarithromycin (MIC >16) and tetracyclines (doxycycline MIC 4; minocycline MIC 2), while susceptibility was maintained toward trimethoprim-sulfamethoxazole (TMP-SMX MIC <=0.25), linezolid (MIC <=1) and beta-lactams (amoxicillin/clavulanate MIC <=2). Therefore, parenteral antibacterial therapy with intravenous linezolid (600 mg every 12 hours) and intravenous TMP-SMX (240/1200 mg every 8 hours) was started with subsequent improvement of signs and symptoms and decreasing inflammatory markers with resolution of fever and progressive reduction of erythema and lesions' size. Combination therapy was chosen according to the severity of the case and fascia involvement. TMP-SMX was interrupted after 5 days for onset of cutaneous rash. Patient was discharged from the hospital after 10 days of parenteral therapy with indication to receive oral therapy with amoxicillin/clavulanate (1 g every 8 hours) and linezolid (600 mg every 12 hours). Three weeks later linezolid was interrupted for anemia, while amoxicillin/clavulanate was prolonged for a total of 5 months. During the follow-up, cellulitis was completely healed with only a few dyschromic scars left (Figure 1, d).

LITERATURE REVIEW

We performed a literature review of cutaneous nocardiosis cases in immunocompetent population. On January 2022 we performed a PubMed search using the following search strings: "Cutaneous" AND "Nocardiosis". 487 papers regarding such topic were identified. Among them, we selected, by abstract or full text reading, 95 articles (case reports and case series) on primary cutaneous nocardiosis in immunocompetent patients. We excluded any article that didn't include at least one case report and cases of infections caused by other pathogens. Furthermore, we excluded cases of non-cutaneous nocardiosis, secondary lesions or disseminated disease and cutaneous nocardiosis in immunocompromised patients (congenital

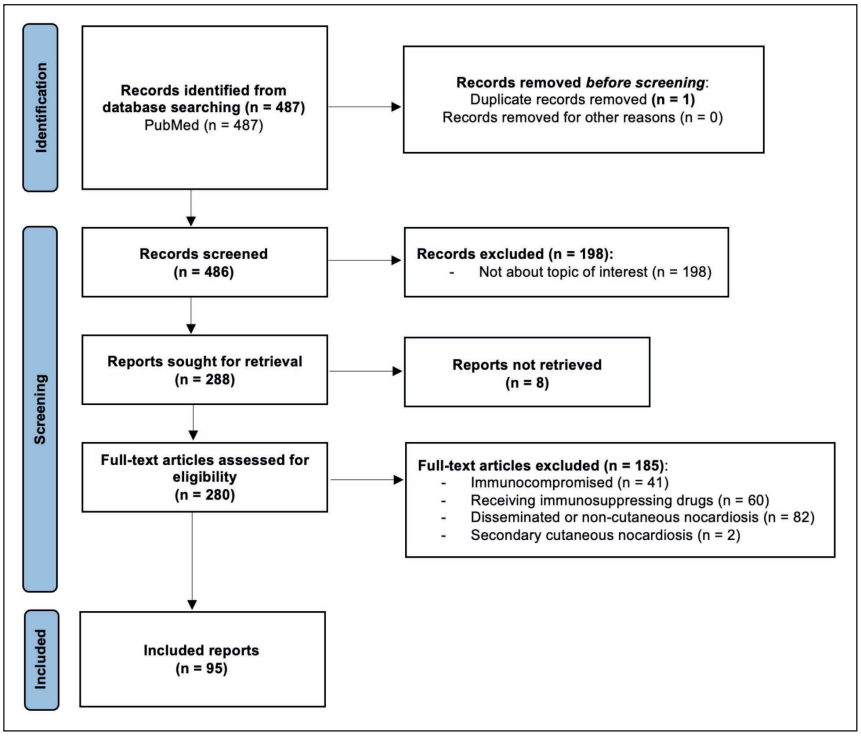

Figure 2 - Flowchart of literature review by searching "cutaneous" and "nocardiosis" on PubMed.

Table 1 - Cases of primary cutaneous nocardiosis following insect bite.

Year	*Country*	*Authors*	*Site of infection*	*Occupation or risk factor for infection*	*Nocardia species*	*Type of cutaneous nocardiosis*
1987	USA	Leggiadro RJ [3]	Neck	Tick bite	*N. brasiliensis*	Lymphocutaneous
1992	USA	O'Connor PT [4]	Leg	Insect bite	*N. brasiliensis*	Lymphocutaneous
1999	Switzerland	Paredes BE [5]	Leg	Insect bite	*N. brasiliensis*	Lymphocutaneous
2001	Germany	Slevogt H [6]	Leg	Insect bite	*N. brasiliensis*	Lymphocutaneous
2001	USA	Fergie J [7]	13 cases; various sites	Insect bite	*N. brasiliensis*	Cutaneous and lymphocutaneous
2004	Australia	Isbister G [8]	Arm	Spider bite	*N. brasiliensis*	Cutaneous
2017	Brazil	Secchin P [9]	Leg	Insect bite	*N. brasiliensis*	Lymphocutaneous
2017	China	Chu L [10]	Arm	Wasp sting	*N. brasiliensis*	Cutaneous
2019	China	Mu YZ [11]	Hand	Insect bite	*N. brasiliensis*	Lymphocutaneous
2021	Switzerland	Acevedo C [12]	Neck	Insect bite	*N. brasiliensis*	Cutaneous

immunodeficiency, HIV infection, hematological diseases, solid tumor or other acquired immunodeficiency) or patients using immunosuppressing drugs (e.g. chemotherapy, long-term steroid therapy, biologic drugs or other immunosuppressor drugs) (Figure 2). As a result, most cases of cutaneous nocardiosis in immunocompetent patients resulted to involve the extremities (arm, hand, or leg) and occurred following a minor trauma, especially during gardening or agriculture work. No differences in severity were observed in immunocompetent patients between infections caused by different Nocardia species, considering that only sporadic cases were determined by species different from *N. brasiliensis*. In fact, *N. brasiliensis* and *N. asteroides* were the most frequent *Nocardia* species isolated (respectively 60% and 10%), in most cases identified by 16s rRNA gene amplification and sequencing laboratory tests (Supplementary Table). *N. brasiliensis* turned out to be more frequently responsible for lymphatic extension of the infection and infections caused by this species were often complicated by abscess formation. More often a chronic presentation was observed and only in few cases there was a rapid progression of disease after primary lesion. Only 10 articles reported episodes of cutaneous or lymphocutaneous nocardiosis as a consequence of an insect bite: 1 from tick bite, 1 after wasp sting, 1 after spider bite and in the other 19 cases the insects were not identified. In all these cases *N. brasiliensis* was isolated from cutaneous samples (Table 1).

DISCUSSION

Primary cutaneous nocardiosis affects more commonly immunocompetent hosts and *N. brasiliensis* is the species isolated in most cases (80%) [2]. Primary cutaneous infections include lymphocutaneous infection, superficial cellulitis, or localized abscess, and usually involve the face in children and the lower extremities in adults. In an immunocompetent individual, they occur 1 to 3 weeks following minor local injury, especially in traumatic outdoor activities (*e.g.* gardeners, farmers, road accidents), with subsequent environmental contamination of the wound [2]. Exceptionally, the infection presents after an insect bite or sting. Clinical signs usually have a slow progression, in weeks or months. Interestingly, in our case a very fast and extensive progression of ascending cellulitis was seen, with the appearance in 3 days of secondary cutaneous lesions and regional lymph-nodes involvement. Indeed, in our case the diagnosis of cutaneous nocardiosis was delayed because it was clinically indistinguishable from skin infections caused by other organisms, such as common pyogenic bacteria, fungi or atypical mycobacteria, as reported in other series. The preferred diagnostic specimen for cutaneous nocardiosis is obtained by skin biopsy. The microbiological diagnosis of these actinomycetes can be challenging because of their slow growth that can take up to 14 days on solid media (laboratory should be informed of the diagnostic suspect

and samples should be incubated up to 2 weeks). Indeed, *Nocardia* may grow on most routine media and blood culture bottles, but specific media can be used to increase sensitivity (*e.g.* buffered charcoal yeast extract). Furthermore, these organisms can be hypothesized obtaining Gram staining, Gomori methenamine silver stain or modified Kinyoun acid-fast staining. The choice and dosage of antimicrobial drugs and the duration of therapy depend on the site and the extent of infection, underlying host factors, the species of *Nocardia*, and the clinical response to initial management. As clinical isolates of *Nocardia* spp. show variable susceptibility to antimicrobials, antimicrobial susceptibility testing should always be performed. TMP-SMX is the cornerstone of nocardiosis therapy, and its total duration should be 3-6 months, but shorter courses may be appropriate in immunocompetent patients [96]. Intravenous multidrug regimen can be used for initial treatment and should be continued for at least 2-6 weeks. Debridement of infected tissues, and incision and drainage of abscesses are often necessary; deep locations may require consultation for interventional radiology-guided evacuation. In our case, antibiotic therapy was continued for 5 months because of infection severity, fascia's involvement, and lack of surgical approach.

In conclusion, primary cutaneous nocardiosis usually develops in immunocompetent host. *N. brasiliensis* is the most common species causing cutaneous or lymphocutaneous disease, as in our case. The real burden of soft-tissues nocardiosis seems low but many cases might go undiagnosed because of difficulties in microbiology diagnosis. Our case suggests that primary cutaneous nocardiosis should be included in the diagnostic pathway in cases of cellulitis following insect bite or sting, especially when localized to extremities.

Conflict of interest

None of the authors have conflict of interest.

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Ethical declaration

The patient gave her written and informed consent for publishing case description and pictures. Authors made every attempt to guarantee the patient's anonymity.

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