

Lymphocutaneous nocardiosis caused by *Nocardia brasiliensis* in an immunocompetent patient: a case report

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Abstract

Nocardia usually manifests as opportunistic infections in immunocompromised hosts. Here, we report a rare case of an immunocompetent patient with lymphocutaneous nocardiosis. The patient was a 34-year-old man presenting with fever, multiple scattered pustules on both upper limbs and several subcutaneous nodules on the left elbow and forearm. Skin biopsy of the subcutaneous nodule revealed suppurative inflammation of the lymph nodes. Pus cultures were finally identified as *Nocardia brasiliensis*. The patient fully recovered without relapse after receiving optimized antimicrobial therapy consisting of linezolid combined with sulfonamides. Nocardiosis is a rare opportunistic disease which may be fatal and usually affects immunocompromised hosts, resulting in suppurative and granulomatous inflammation. *Nocardia* has a long culture cycle, is difficult to diagnose, and is more likely to be neglected in healthy young people. The present case suggests that physicians should be aware that nocardiosis is a differential diagnosis to consider in patients with suppurative infection, especially when anti-infective treatment is ineffective.

Keywords

Nocardia brasiliensis, immunocompetent, lymphocutaneous nocardiosis, suppurative infection, opportunistic infection, antimicrobial therapy

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Background

The genus *Nocardia* are actinomycetes widely distributed in the environment. Contact with humans usually manifests as an opportunistic infection in immunocompromised hosts, especially individuals who have undergone solid organ transplantation, patients with HIV/AIDS, or patients receiving long-term treatment with corticosteroids or immunosuppressive drugs.^{1,2} However, *Nocardia* species sometimes infect healthy individuals. Here, we report a case of lymphocutaneous nocardiosis caused by *Nocardia brasiliensis* in an immunocompetent young man.

Case presentation

In November 2015, a 34-year-old Chinese man who had fever with multiple pustules on both limbs for 5 days was referred to the Infectious Diseases Division of the First People's Hospital of Hangzhou.

Five days earlier, the patient was feverish with a high temperature of 39°C and experienced dizziness and nausea but no vomiting, chills, or cough and sputum. His fever was

followed by erythematous swelling of the fingers and left wrist. The patient was otherwise healthy and remembered no episode of injury. The only relevant history was that he had been to a dental clinic 5 days earlier. Despite a 4-day course of antibiotic therapy (cefotaxime + ornidazole), his symptoms worsened. Erythematous swelling of the fingers and left wrist developed, accompanied by white maceration, shallow ulcers and pustules, with spreading subcutaneous nodules along both forearms. Considering the possibility of drug-resistant bacterial infection, treatment with vancomycin combined with piperacillin sulbactam was selected. However, the patient's symptoms did not improve significantly.

Physical examination revealed a heart rate of 100 beats/minute, blood pressure of 121/77 mmHg, respiratory rate of 20 breaths/minute, temperature of 38.2°C, numerous 1 × 2 cm pustules on the fingers and left wrist (Figure 1a), and several subcutaneous nodules on the left elbow and forearm. The largest nodule measured 4 × 5 cm (Figure 1b).

Laboratory investigations revealed a white blood cell count of $15.3 \times 10^9/L$ (reference

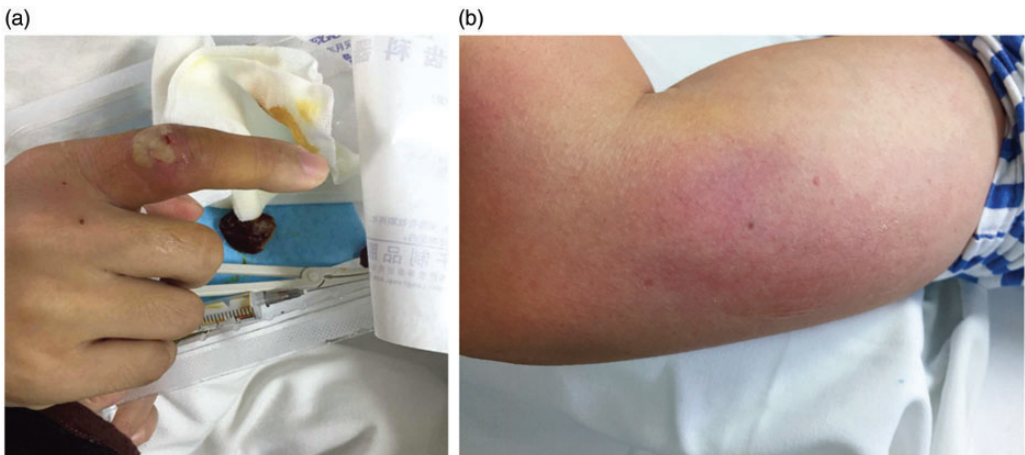


Figure 1. (a) Clinical features at first visit. Erythematous swelling of the right index finger was observed, accompanied by white maceration and pustules. (b) Clinical features at first visit. Erythematous swelling of the left elbow observed, accompanied by a subcutaneous nodule approximately 4 × 5 cm in size.

range: $3.5\text{--}9.5 \times 10^9/\text{L}$) (78.7% neutrophils), C-reactive protein of 64 mg/L (reference range: 0–8 mg/L), and normal procalcitonin. Urinalysis results were within normal limits. A purified protein derivative skin test for tuberculosis was negative. Antinuclear antibodies, rheumatoid factors, tumour markers, HIV and syphilis tests were all negative. Chest computed tomography showed no obvious abnormalities. Ultrasonography of the subcutaneous nodule on the right elbow suggested a swollen lymph node. Next, histology of a skin biopsy taken from the subcutaneous nodule of the left elbow was

performed. The result showed abscess formation in the lymph nodes (Figure 2a). Pus cultures on blood agar plates grew heaped, chalky white colonies (Figure 2b). Gram staining revealed Gram-positive organisms; microscopically, the organisms were slender rods with many branches (Figure 2c–d). The organism was finally identified as *Nocardia brasiliensis* by matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) and 16S rRNA gene sequencing. The diagnosis was amended and treatment was changed immediately to 600 mg linezolid every 12 hours combined

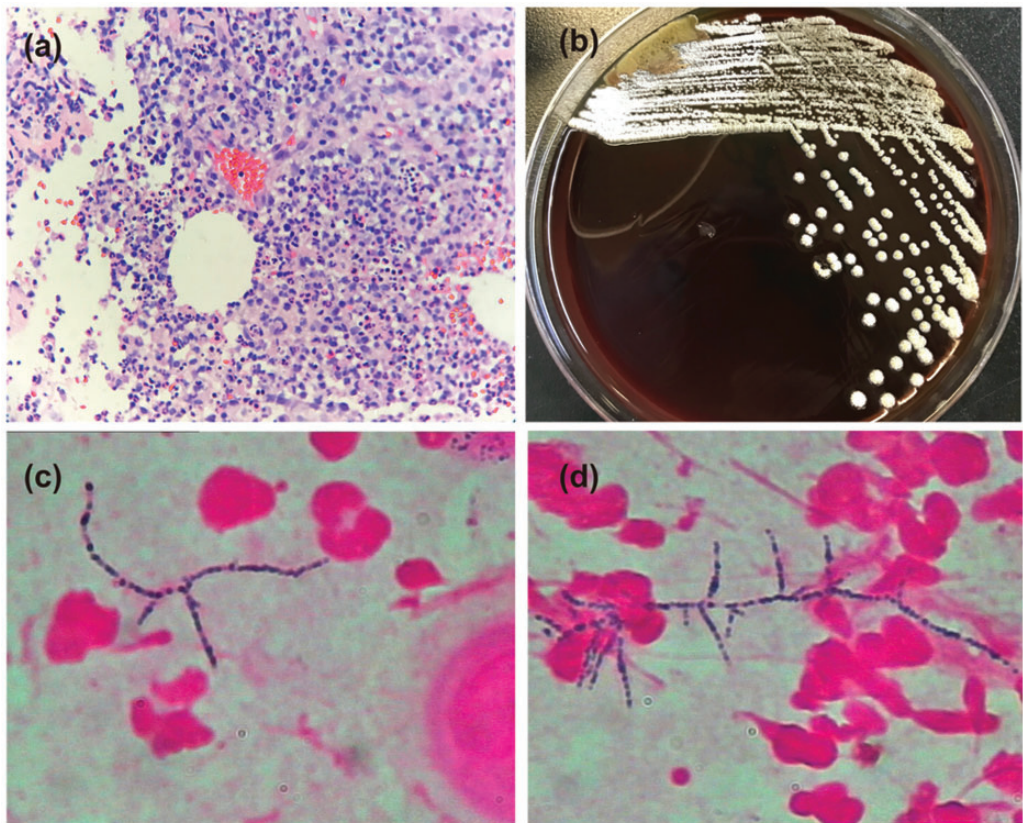


Figure 2. (a) Histopathological findings. A skin biopsy taken from the largest subcutaneous abscess of the left elbow revealed a significant inflammatory cell infiltration, with abscess formation and giant cells in lymph node tissue (haematoxylin and eosin, $\times 200$). (b) Colony culture. A small number of chalky white colonies formed on a blood agar plate. (c, d) A smear of the bacteria from a cultured colony. Gram-positive rods with long, sinuous branches were observed (Gram stain, $\times 1000$).

with trimethoprim-sulfamethoxazole (TMP-SMX, 80/400 mg, three tablets three times a day) for 2 weeks. This treatment produced complete resolution of the lesions, and TMP-SMX monotherapy was continued for 6 weeks. There was no subsequent recurrence.

Susceptibility testing was performed using the Etest method. We subcultured the *N. brasiliensis* isolate on sheep blood agar plates and, after 96 hours, inoculated the isolate into broth to a turbidity equivalent of 0.5 McFarland standard as measured using a densitometer (Densimat; bioMérieux, Marcy l'Etoile, France). The inoculum was spread on Mueller-Hinton agar. After incubating for 96 hours at 37°C in ambient air, the minimum inhibitory concentrations (MICs) were recorded as the values at which the inhibition zone intercepted the scale on the Etest strip (Bio-kont, Zhejiang, China). The MICs are shown in Table 1 and were interpreted according to the CLSI M24-A2 recommendations.³

Table 1. Antimicrobial susceptibility testing results for *Nocardia brasiliensis*.

Antimicrobial agent	MIC*, µg/mL	Tentative interpretation
Imipenem	32	R
Gentamicin	0.064	S
Tobramycin	0.064	S
Cefotaxime	256	R
Cefepime	256	R
Ceftriaxone	256	R
Amoxicillin-clavulanic acid	0.25	S
Amikacin	0.5	S
Linezolid	0.5	S
Clarithromycin	0.125	S
Trimethoprim-sulfamethoxazole	0.064	S
Doxycycline	0.125	S
Ciprofloxacin	32	R
Minocycline	0.064	S

I = intermediate, MIC = minimum inhibitory concentration, R = resistant, S = susceptible.

*MICs were determined by the E-test method and interpreted according to the CLSI M24-A2 recommendations.³

Discussion

Nocardiosis is a rare opportunistic disease that is potentially fatal and mainly affects the lungs, skin and central nervous system, resulting in suppurative and granulomatous inflammation.⁴ The infection can be systemic or cutaneous.

Cutaneous nocardiosis can be divided into primary cutaneous nocardiosis and secondary cutaneous nocardiosis caused by haematogenous dissemination. In contrast to other types of nocardiosis, primary cutaneous disease can develop in immunocompetent hosts with a history of trauma and can be further divided into three major subtypes: (1) actinomycetoma, (2) superficial skin infection, and (3) lymphocutaneous.⁵ Currently, *N. brasiliensis* accounts for the majority of cutaneous infections. After skin infection, an abscess or localized cellulitis can form on the surface of the skin. If the infection spreads to regional lymph nodes, painful multiple erythematous nodules or satellite pustules may develop and be distributed along the lymphatic tract.⁵⁻⁷ This form of nocardiosis is called lymphocutaneous nocardiosis. Patients often have a recent history of trauma, and the lower limbs are affected quite commonly. Given the similar presentation of sporotrichosis, lymphocutaneous nocardiosis is often called sporotrichoid nocardiosis. Sporotrichosis is the main differential diagnosis.^{8,9}

Nocardia species dwell in the soil, often invading the skin through open wounds during gardening activities. Another transmission route is through infected animals.^{5,7,8} So far, there have been only two cases reported in China of lymphocutaneous nocardiosis caused by *N. brasiliensis* in immunocompetent patients. One was reported by Chu et al.¹⁰ in 2017 and occurred in an 87-year-old woman following a wasp sting. Another case was reported by Zhang et al.¹¹ in 2019 and occurred in a 42-year-old woman following an unknown

insect bite. In this present case, the patient was finally diagnosed with the lymphocutaneous type of primary cutaneous nocardiosis caused by *N. brasiliensis*. This is the first report of this condition in a healthy young man in China. By contrast with previous reports, the patient had no history of trauma or garden work. Although he had a history of dental work before the onset, it was difficult to explain his cutaneous infection.

Considering that antibiotic sensitivity varies among *Nocardia* species, it is important to accurately discriminate these organisms at the species level.¹² Identification of *Nocardia* species is often performed using molecular techniques such as PCR restriction enzyme analysis and 16S rRNA gene sequencing. MALDI-TOF MS-based identification is a potentially rapid and inexpensive alternative.^{13,14} In the current case, the isolate was identified by MALDI-TOF MS and this result was confirmed by 16S rRNA gene sequencing.

All cases of nocardial infection should receive treatment, including cases in immunocompetent patients with localized cutaneous disease.¹⁵ Nocardial infections frequently call for prolonged therapy. Monotherapy with TMP-SMX has evolved towards initial combination drug therapy for most forms of nocardiosis.¹⁶ For patients with central nervous system involvement, disseminated infection and serious disease, a three-drug regimen comprising TMP-SMX, amikacin, and either ceftriaxone or imipenem is recommended.^{17,18} For immunocompetent patients with all forms of cutaneous nocardiosis, TMP-SMX monotherapy or in combination with another antibiotic may be adequate. Mycetoma, some ocular infections, deep abscesses and rare cases with other body sites involvement may require surgical treatment.¹⁸

Antimicrobial susceptibility tests are especially important for guiding treatment choices. Multidrug resistant strains of *N. brasiliensis* are common. In a study in

Spain, susceptibility testing of 39 strains of *N. brasiliensis* showed that the species was susceptible to TMP-SMX, linezolid and amikacin. Low resistance rates (7.7% to 12.8%) were observed against amoxicillin/clavulanic acid, tobramycin and cefotaxime, whereas high rates (56.4% to 82.1%) were recorded for imipenem, minocycline, ciprofloxacin and erythromycin.⁴ These results were similar to some past studies.^{19,20} Linezolid is a welcome and useful addition to the treatment options for nocardiosis and has excellent potential as a second-line agent. This drug may also be especially useful as initial therapy until susceptibility results for other potential agents are available, and it has become an attractive alternative to TMP-SMX, imipenem, or amikacin for empirical treatment.^{4,21}

When we started treatment for the present case, the susceptibility results of this strain were not available. Referring to the results of antibiotic sensitivity from the above studies, we empirically chose linezolid and TMP-SMX as the initial combination therapy and achieved a good therapeutic result. Later, the susceptibility results showed that this isolate was sensitive to TMP-SMX, linezolid, amikacin, amoxicillin-clavulanic acid and clarithromycin, but resistant to Imipenem, cefotaxime and ciprofloxacin. Therefore, this strain was classified as multidrug resistant.

The duration of therapy for nocardiosis is variable and depends on the clinical condition and the patient's immune status. Three months of treatment is proposed for a primary cutaneous disease, and in cases of mild disease with a quick and complete improvement, a shorter treatment course of 1 month is possible. However, mycetoma requires more prolonged therapy.¹⁸ Six months to 1 year is recommended for visceral or systemic nocardiosis.¹³

Nocardia has a long culture cycle and is difficult to diagnose. It is more likely to be neglected in healthy young people. Therefore, nocardiosis should be excluded, especially

for suppurative infections with poor therapeutic effects.

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Author contributions

SL and XX wrote the case report; MW and JZ took care of the patient; PC and JD took part in the drafting; SW conducted bacterial identification and antimicrobial susceptibility testing; JJ revised the manuscript and reviewed the final manuscript; all authors read and approved the final version of the manuscript.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. The patient understood that the text and any images published in the article will be freely available on the internet and may be seen by the general public.

Declaration of conflicting interest


The authors declare that there is no conflict of interest.

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