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Nocardia wallacei: A rare cause of actinomycetoma in an immunocompetent patient

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CASE STUDY

ABSTRACT

Actinomycetoma, a neglected tropical disease affecting the skin and soft tissues, is primarily caused by filamentous bacteria including *Nocardia* species. Here, we report a healthy 56-year-old man who has a one-year history of nodular lesions with seropurulent discharge on his right knee. Despite negative initial tissue culture, the sulfur granules that were partially acid-fast and Gram-positive branching filamentous rods were revealed in the tissue section. Repeated investigation identified the rare pathogen *Nocardia wallacei,* using matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) and 16S ribosomal ribonucleic acid (rRNA) gene sequencing. The patient was successfully treated with a six-month course of trimethoprim-sulfamethoxazole.

This report describes a rare case of actinomycetoma due to *N. wallacei,* highlighting the challenges in diagnosis and the importance of accurate pathogen identification for the successful management of infection. The current literature regarding the causative agent will also be discussed.

KEYWORDS

actinomycetoma, *Nocardia wallacei*, neglected tropical disease, MALDI-TOF MS, immunocompetent, nocardiosis

INTRODUCTION

Mycetoma is a chronic, localized granulomatous infection of the skin and subcutaneous tissue with potential extension to underlying muscle, cartilage, or bone. It is characterized by a triad of tumefaction, draining sinuses, and grain-like discharge [1]. Etiological classification divides it into two subtypes, including eumycetoma—caused by true fungi—and actinomycetoma—caused by filamentous bacteria with *Actinomadura madurae, Streptomyces somaliensis, Actinomadura pelletieri, and Nocardia brasiliensis* being most common [1, 2]. In most cases, the infection occurs when the causative organisms are directly inoculated into the skin following minor trauma [1, 2]. The foot is the most common site of infection, followed by the legs, trunk, and arms [2]. Characteristic grains indicate a compact mass of fungal colonies or clumped filamentous bacteria, varying in size and color based on their causative agents [1]. Although the clinical characteristics of both forms are similar and can cause significant dysfunction and disfigurement, actinomycetoma is more common and generally has a better prognosis. However, treatment is challenging and frequently requires prolonged antimicrobial therapy [1].

The prevalence of mycetoma varies according to region; higher prevalence rates are found in tropical and subtropical areas, particularly in hot and dry climates. Eumycetoma is common in Africa, while actinomycetoma is more prevalent in Middle and South America [2]. The prevalence of mycetoma is higher in Mauritania and Sudan, with over 1 in 100,000

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reported cases, compared to significantly lower rates in Asian countries like India and Thailand [2].

Here, we report a case of actinomycetoma caused by rare *Nocardia wallacei* in an immunocompetent Thai patient. Despite negative initial cultures, significant histopathological findings resulted in further molecular testing and imaging, which validated the diagnosis and highlighted the importance of re-evaluation. Also, there will be a discussion on the current literature regarding the causative agent, *N. wallacei*.

CASE PRESENTATION

A 56-year-old man presented with a one-year history of skin lesions on his right knee. Following a history of bumping his knee on his car's running board, the lesion initially appeared as a nontender, solitary papule. The lesion subsequently progressed and ulcerated. Despite previous treatment with antibiotics (amoxicillin and dicloxacillin) and an antifungal (itraconazole) for a minimum of three months at a local clinic, the skin lesions had not shown improvement. The patient had no underlying disease and was a non-drinker and non-smoker. He was employed as an officer and had no history of gardening.

Physical examination revealed hyperkeratotic erythematous plaques with crusted lesions on the right knee, accompanied by surrounding soft tissue swelling (Fig. 1a and b). There was neither lymphadenopathy nor fever at the time of examination. An initial plain film of the right knee suspected the presence of a minimal amount of suprapatellar joint effusion, with no overt bony destruction. Based on the patient's history and physical examination, several conditions were considered in the differential diagnosis, including skin infections such as actinomycetoma, eumycetoma, and non-mycobacterial tuberculosis skin infections. Consequently, the empirical antibiotic treatment was adjusted to include clarithromycin and ciprofloxacin.

Histological examination of biopsy samples taken from the lesion on day 0 showed pseudoepitheliomatous hyperplasia together with suppurative inflammation within the dermis and subcutis (Fig. 1c). The granules surrounded by a mix of inflammatory cells and the Splendore-Hoeppli phenomenon were evident as key findings (Fig. 1d). Due to the thin, fine filament nature of these granules, a differential diagnosis between actinomycetoma and eumycetoma was necessary. Gram- (Fig. 1e) and modified acid-fast (Fig. 1f) staining of the skin tissue revealed Gram-positive and

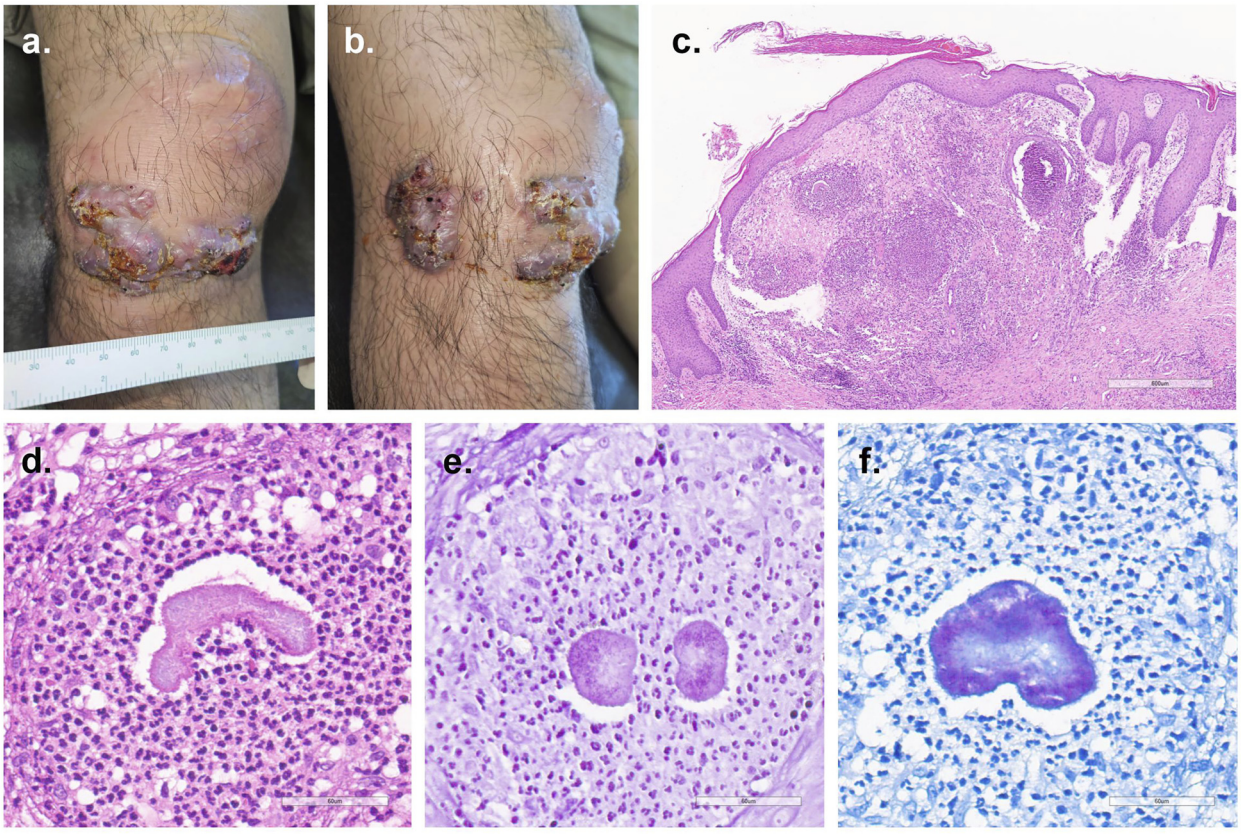

Fig. 1. Multiple firm erythematous plaques with crusting and surrounding inflammation on the right knee **(a, b)**. Histopathological features **(c)** reveal pseudoepitheliomatous hyperplasia of the epidermis with suppurative foci in the dermis [hematoxylin and eosin (H&E) stain, 40× original magnification]. The granule is surrounded by mixed inflammatory cells and the presence of Splendore-Hoeppli phenomenon **(d)** (H&E, 400× original magnification). Gram- **(e)** and modified acid-fast **(f)** stained histological section showing Gram-positive fine filamentous within the granules in the same field (400× original magnification)

weakly acid-fast bacilli, respectively. However, tissue cultures for bacteria, fungus, and mycobacteria were negative.

At a follow-up visit (day +14), some lesions exhibited decreased induration and were dry; however, there was increased inflammation, along with the development of cellulitis and new abscesses. To identify the causative agent, especially for filamentous bacteria, repeated cultures of the exudate from the sinus were performed. We utilized the International *Streptomyces* Project (ISP)-2 medium [3], which contained 4 grams (g) of yeast extract (Becton Dickinson-Sparks, Maryland, United States), 10 g of malt extract (Oxoid Limited, Hampshire, United Kingdom), 4 g of glucose (Merck KGaA, Darmstadt, Germany), 20 g of granulated agar (Becton Dickinson-Sparks, Maryland, United States), and 100 micrograms per milliliter (μg mL^{-1}) of nalidixic acid (AppliChem GmbH, Darmstadt, Germany). In addition, chocolate agar, which was composed of gonococcal (GC) agar base (Oxoid Limited, Hampshire, United Kingdom) supplemented with soluble hemoglobin powder (Oxoid Limited, Hampshire, United Kingdom), was used to support the growth of fastidious organisms. On day +17, chalky white colonies of varying sizes, exhibiting dry, rough, and flaky texture, were observed on ISP-2 medium (Fig. 2a) and chocolate agar (Fig. 2b). Under oil microscopy, numerous beaded, branching filamentous gram-positive bacilli that fragmented into rod-shaped forms were observed in the gram staining (Fig. 2c) and modified acid-fast staining (Fig. 2d), which was compatible with *Nocardia* species [4].

Using matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) with VITEK® MS system (bioMérieux SA, Marcy-l'Étoile, France), the clinical isolate was identified as *N. wallacei*. A parallel specimen was also submitted for species confirmation by 16S ribosomal ribonucleic acid (rRNA) gene sequencing. Deoxyribonucleic acid (DNA) extraction of bacterial cells was performed using NucleoSpin® Microbial DNA kit (MACHEREY-NAGEL GmbH & Co. KG, Düren, Germany). The polymerase chain reaction (PCR) amplification was performed on extracted DNA using the primer pair 27F (5′-AGAGTTTGATCMTGGCTCAG-3′) and 1492R (5′-GGTTACCTTGTTACGACTT-3′) (Macrogen Inc., Seoul, Republic of Korea). The purified PCR products were obtained with the NucleoSpin® Gel and PCR Clean-up kit (MACHEREY-NAGEL GmbH & Co. KG, Düren, Germany) and submitted for sequencing at Macrogen, Inc. (Seoul, Republic of Korea). The results demonstrated 99.80%

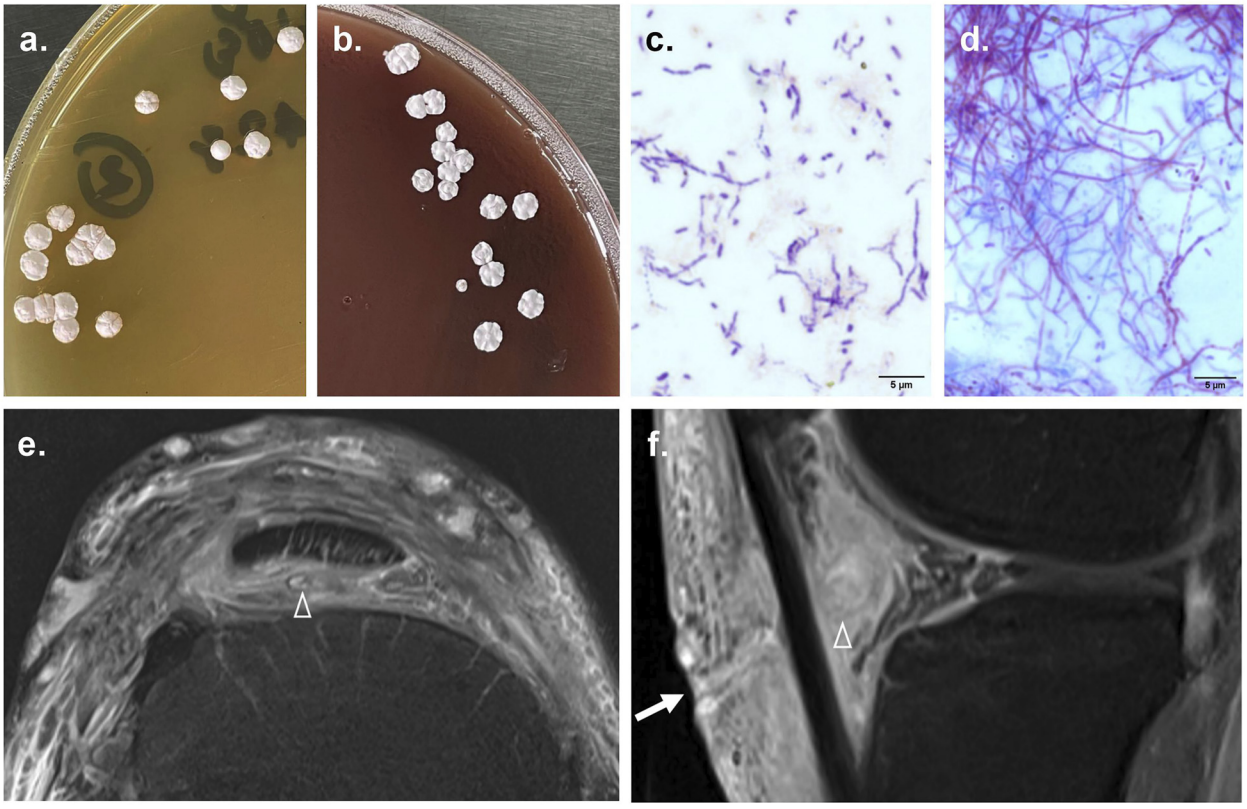

Fig. 2. During the follow-up visit, the exudative cultures exhibited chalky white colonies on both International *Streptomyces* Project (ISP)-2 medium **(a)** and chocolate agar **(b)**, with characteristic of Gram-positive **(c)** and partially acid-fast filamentous bacilli **(d)** (bar = 5 μm). Magnetic resonance imaging (MRI) findings of the knee on axial fat-suppressed T2-weighted image **(e)** and sagittal contrast-enhanced fat-suppressed T1-weighted image **(f)** show multiple small, round-to-oval hyperintense lesions separated by peripheral hypointense tissue in the skin and subcutaneous tissue, extending into the Hoffa fat pad. A lesion in the Hoffa fat pad contains a central hypointense dot, resulting in the 'dot-in-circle' sign (arrowhead). Surrounding hyperintense inflammatory changes are observed. There is a sinus tract in the infrapatellar region of the anterior knee, opening to the skin (arrow in Image f)

similarity to the reference strain *N. wallacei* ATCC 49873 and 99.71% similarity to *N. wallacei* strain W8083. Additionally, it revealed a high similarity of 98.24% to *Nocardia transvalensis*.

A definite diagnosis of actinomycetoma caused by *N. wallacei* was established; a double-strength tablet of 160 mg trimethoprim plus 800 mg sulfamethoxazole (TMP-SMX) was administered twice daily (day +21), as it is regarded as the first-line treatment for cutaneous nocardiosis [5]. Additionally, magnetic resonance imaging (MRI) results of the right knee, performed on day 42 post-initial assessment, revealed multiple small round lesions involving the skin and subcutaneous tissue with a sinus tract in the infrapatellar region of the anterior knee, extending into Hoffa's fat pad. Some of the lesions exhibited a 'dot-in-circle' sign, consistent with mycetoma (Fig. 2e and f).

Following a treatment duration of 2.5 months with TMP-SMX (day +98), the clinical condition showed marked improvement. There was no new abscess or progression of cellulitis. The treatment continued, and upon follow-up at 4.5 months (day +161), the lesions exhibited healing with resultant scar formation. Additionally, a follow-up MRI (day +161) revealed a complete resolution of the disease. Consequently, the treatment was discontinued after a total of six months (day +206). The patient was subsequently monitored for an additional three months after the cessation of treatment (day +290), during which no new lesion developed.

Ethical approval and consent for publication

The current study has been approved by the Ethics Committee of the Faculty of Medicine, Chiang Mai University. (Approval number: MIC-2567-0529). Written informed consent has been obtained from the patient for publication of his data and photographs.

DISCUSSION

We describe a case of an immunocompetent patient who was diagnosed with actinomycetoma caused by *N. wallacei*. The patient exhibited an indolent subcutaneous infection that had not improved despite previous antibiotics and antifungal treatments. With the current approach, even though tissue cultures were negative, the presence of sulfur granules in histological examinations led to the suspicion of actinomycetoma. This was further supported by the presence of Gram-positive and partially acid-fast-stained branching filaments found within the granules. Several infectious diseases that cause grain production should be included in differential diagnosis, such as eumycetoma and botryomycosis (infections caused by *Staphylococcus aureus* that result in grain contents containing cocci) [1]. Although the dot-in-circle sign on MRI is specific for mycetoma, it is less sensitive and cannot differentiate between actinomycetoma and eumycetoma [1].

Microbiological techniques are crucial for a conclusive diagnosis, as *Nocardia* species can be challenging to cultivate. MALDI-TOF MS and 16S rRNA sequencing are reliable identification techniques. According to our findings, 16S rRNA sequencing demonstrated a high identity range of 99.71–99.80% with strains of *N. wallacei,* thereby confirming the accuracy of MALDI-TOF MS. When conventional tissue cultures yield negative results and previous treatments have failed, combining the sequencing technique with MALDI-TOF MS can improve diagnostic performance.

Nocardia are aerobic, Gram-positive, filamentous branching bacteria belonging to the *Actinomycetales* order and can cause nocardiosis, which includes localized skin infections as well as severe pulmonary and disseminated infections affecting the central nervous system and other organs [6–8]. *Nocardia asteroides* complex, *N. brasiliensis, Nocardia nova,* and *Nocardia farcinica,* are the main pathogens [9]. Typically, the *N. asteroides* complex is associated with more serious pulmonary infections and hematogenous dissemination, while *N. brasiliensis* typically causes primary skin infection [9]. Despite the increasing prevalence of infections with *Nocardia* species, those caused by *N. wallacei* remain relatively rare, with a limited number of documented cases to date (Table 1). This pathogen can infect both immunocompromised and immunocompetent hosts. Some cases of *N. wallacei* infection can lead to disseminated infection and may be fatal. However, few clinical features have been documented as actinomycetoma.

N. wallacei is classified within the *N. transvalensis* complex. Based on DNA-DNA hybridization techniques and molecular phylogenetic analysis of the 16S rRNA gene, the *secA1* (essential secretory protein SecA1) gene, and *hsp65* (65-kilodalton heat shock protein) gene, it was formally recognized as a new species in 2008 [10]. Additionally, it was determined to possess the drug susceptibility pattern type IV of *N. asteroides*, which has important clinical and taxonomic implications. This pattern is characterized by high resistance to all aminoglycosides but susceptibility to ciprofloxacin [9–11]. Unlike most *Nocardia* species, *N. wallacei* has been reported to show resistance to all aminoglycosides, including amikacin [12–14], due to the presence of an aminoglycoside-modifying gene known as *warA* (wallacei amikacin resistance A) [12]. Furthermore, while many *Nocardia* species exhibit mutations in the *gyrA* (DNA gyrase subunit A), such as Ser83Ala substitution associated with resistance to ciprofloxacin, *N. wallacei* still demonstrates high susceptibility to ciprofloxacin (83%) [13]. Consequently, a partial response to ciprofloxacin was observed in this patient.

Our case exhibited complete resolution of clinical manifestations and radiographic improvement after six months receiving TMP-SMX monotherapy. Despite a recent case report highlighting actinomycetoma caused by multidrug-resistant *N. wallacei* [15], TMP-SMX remains the gold standard for treatment of actinomycetoma, whether used alone or in combination with amikacin, dapsone, or rifampicin, based on the severity of the disease and the causative agents [1]. This effectiveness could be due to its lipophilic property, which enables effective penetration into the tissue [16]. According to a recent multicenter retrospective study [5], TMP-SMX has shown a susceptibility rate ranging from 90% to 100% against

Table 1. Types of infections caused by *Nocardia wallacei* classified by immune status*: Case reports

Types of Infection	Author(s) (year)	Patient Demographics	Identification Methods	Treatment (duration)	Outcomes	Notes
Skin and Soft Tissue Infection			**Immunocompetent**			
	Welsh et al. 2018 [15]	18, M (Mexican)	Tissue culture, partial 16S rRNA, and analysis of *secA1* gene sequencing	Linezolid 1.2 g/day (3 months)	Cured	Actinomycetoma of the left leg
	Rojas et al. 2017 [17]	45, M (Venezuelans)	Culture and 16S rRNA sequencing	TMP-SMX 160/800 mg/day (12 months)	N/A	Actinomycetoma of back
	Qin et al. 2023 [18]	59, F (Chinese); COPD	mNGS of abscess	TMP-SMX 640/3,200 mg/day (at least 2 months)	Improved	Back abscess and co-infection with *Mycobacterium abscessus* pneumonia
			Immunocompromised: N/A			
Lung Infection			**Immunocompetent**			
	Pan et al. 2024 [19]	61, F (Chinese)	MALDI-TOF MS of BALF	Linezolid 1.2 g/day (6 months)	Improved	–
	Ranjan et al. 2024 [20]	75, M (Indian); type 2 DM and epilepsy	16S rRNA sequencing of sputum	Empirical antibiotics	Against medical advice	–
			Immunocompromised			
	Gonzalez-Nava et al. 2016 [21]	43, M (Mexican); HIV	Culture and 16S rRNA sequencing of sputum	N/A	N/A	–
	Hamid et al. 2013 [4]	54, M (Saudi Arabian); HIV	16S rRNA sequencing of BALF	Sulfonamide	Improved	–
	Conville et al. 2008 [10]	57, M (American); carcinoma of tongue and PCP	REA of a portion of the 65-kDa heat shock protein gene of pleural fluid and sputum	TMP-SMX (4 months)	Died	–
Brain Infection			**Immunocompetent**			
	Corsini Campioli et al. 2021 [22]	73, F (American)	Cultures, 16S rRNA sequencing, MALDI-TOF MS of brain aspiration	Linezolid, TMP-SMX, and minocycline (308 days)	Relapsed and died	–
			Immunocompromised: N/A			
Disseminated Infection			**Immunocompetent**			
	Sithamraju et al. 2020 [8]	46, M (African American)	16s rRNA sequencing of lymph node aspiration	TMP-SMX, imipenem-cilastatin and amikacin	Improved	Involvement of lungs, brain, and lymph nodes
	Cooper et al. 2014 [6]	42, M (Hispanic)	16s rRNA sequencing of brain and lung cavitary lesions from autopsy	Empirical antibiotics and amphotericin B	Died	Involvement of lungs and brain
	Cassir et al. 2013 [7]	62, W (French)	16S rRNA sequencing of BALF and brain specimens	TMP-SMX 480/2,400 mg/day, Linezolid 1.2–3 g/day, and switch to moxifloxacin 400 mg/day (6 months)	Improved	Involvement of lungs and brain

(continued)

Table 1. Continued

Types of Infection	Author(s) (year)	Patient Demographics	Identification Methods	Treatment (duration)	Outcomes	Notes
			Immunocompromised			
	Corsini Campioli et al. 2021 [22]	80, M (American)[#]	Cultures, 16S rRNA sequencing, MALDI-TOF MS of brain aspiration	Moxifloxacin and amikacin (84 days)	Died	Involvement of lungs and brain
	Corsini Campioli et al. 2021 [22]	63, M (American)[#]	Cultures, 16S rRNA sequencing, MALDI-TOF MS of blood and brain aspiration	TMP-SMX and imipenem (20 days)	Died	Involvement of lungs and brain
	Palomba et al. 2022 [23]	80, M (Italian); Waldenstrom macroglobulinemia/ lymphoplasmacytic lymphoma	Culture of brain biopsy	TMP-SMX 15 mg/ kg/day, linezolid 1.2 g/day and switch to minocycline 200 mg/day and TMP-SMX 320/1,600 mg/day (12 months)	Improved	Involvement of lungs and brain

[*]The immune status has been categorized according to the findings described in Corsini Campioli et al. 2021 [22].
[#]Indicates immune status referenced from Corsini Campioli et al. 2021 [22].
Abbreviations: 16S rRNA, 16S ribosomal ribonucleic acid; BALF, bronchoalveolar lavage fluid; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; F, female; g, gram; HIV, human immunodeficiency virus; kDa, kilodalton; kg, kilogram; M, male; MALDI-TOF MS, matrix-assisted laser desorption ionization-time of flight mass spectrometry; mg, milligram; mNGS, metagenomic next-generation sequencing; N/A, not applicable; PCP, pneumocystis pneumonia; REA, restriction endonuclease analysis; *secA1*, essential secretory protein SecA1; TMP-SMX, trimethoprim-sulfamethoxazole.

all *Nocardia* strains. The efficacy of TMP-SMX monotherapy and combination regimens for treating nocardiosis has been demonstrated, with cure rates up to 95.4% [5]. Therefore, TMP-SMX is the preferred primary treatment for most patients, especially for those with skin and soft tissue nocardiosis [5]. Treatment often requires a prolonged duration of over three to six months; however, extended courses may be needed for individuals with widespread infections or severe immunocompromised conditions [5]. Regular patient monitoring is crucial to assess clinical responses and adverse events, allowing for adjustments in treatment duration based on clinical progression and cost-effectiveness.

A significant limitation of our study is the lack of antibiotic susceptibility testing due to the inability to routinely perform minimum inhibitory concentrations (MIC) testing for *Nocardia* spp. It is only conducted in certain cases that are severe or unresponsive to therapy. Due to the slow growth of these organisms, it can be challenging to perform and interpret MIC testing, potentially causing delays in necessary treatment. Furthermore, there are limited studies correlating *in vitro* data with clinical outcomes [5]. However, given the emergence of multidrug-resistant *N. wallacei*, it is essential to include MIC testing in future studies. Such testing should be considered a standard practice to ensure effective antimicrobial therapy and enhance our understanding of susceptibility patterns.

In conclusion, we present the unusual case of actinomycetoma caused by *N. wallacei* in an immunocompetent individual. Accurate diagnosis, including identifying the causative agent and having a comprehensive understanding of patient factors, is essential for identifying at-risk individuals and ensuring effective treatment.

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Material preparation, data collection, and analysis: PC, KD, IK, ST, and TK.

Writing—original draft: PC.

Designed and prepared figures: PC, IK, and TK.

Writing—review and editing: PC, KD, IK, ST, and TK.

Read and agreed to the published version of the manuscript: PC, KD, IK, ST, and TK.

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