Case Report

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Microbiology Section

The Silent Invader: A Case Report of Pulmonary and Cerebral Nocardiosis by *Nocardia cyriacigeorgica* in a Renal Transplant Recipient

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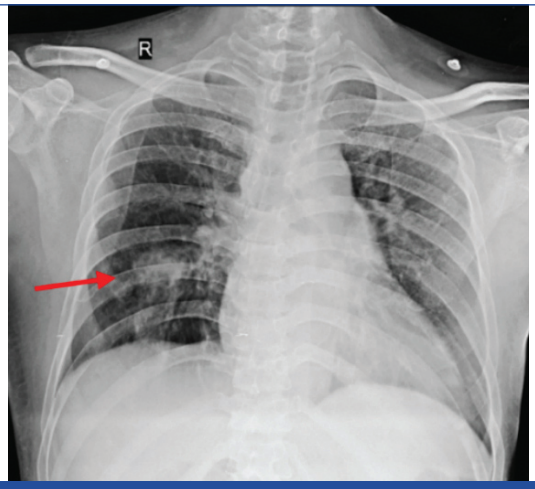
ABSTRACT

Nocardia species primarily affect the lungs of immunocompromised individuals. The clinical presentation may mimic pulmonary tuberculosis. Accurate identification and high clinical suspicion are crucial for correct diagnosis and treatment, especially in tuberculosis-endemic regions. A prolonged antibiotic regimen with two or more drugs is needed, and non adherence to the treatment protocol can lead to potentially fatal outcomes. A 37-year-old man with systemic hypertension and chronic kidney disease, who also underwent live-related renal transplantation, presented with fever, cough, and weight loss. No other significant complaints were noted. Physical examination revealed elevated body temperature and bilateral basal crepitations. Baseline investigations showed anaemia, leukopenia and elevated renal parameters. A chest X-ray indicated right lower zone opacity. A provisional diagnosis of pulmonary tuberculosis or mycosis was considered. Video bronchoscopy revealed thick mucoid secretions that were collected for staining, culture, and sensitivity testing. Gram stain and modified Acid-Fast Bacilli (AFB) stain showed microscopic features suggestive of *Nocardia* species, while the colonies that grew on culture were identified as *N. cyriacigeorgica*. Treatment was initiated with oral cotrimoxazole and intravenous imipenem. After 14 days, he was discharged with a continuation plan but did not adhere to the regimen. The patient eventually presented again 10 days later with seizures and altered sensorium, leading to a diagnosis of cerebral nocardiosis. Despite treatment, he progressed to septic shock and died. Effective treatment of nocardiosis requires a multidrug regimen, typically consisting of cotrimoxazole, amikacin, or imipenem, tailored to the severity of the infection. Early diagnosis, prompt treatment, and strict adherence to protocols are mandatory for successful treatment, as delays or non compliance can lead to fatal outcomes.

Keywords: Brain abscess, Immunocompromised, Opportunistic infection

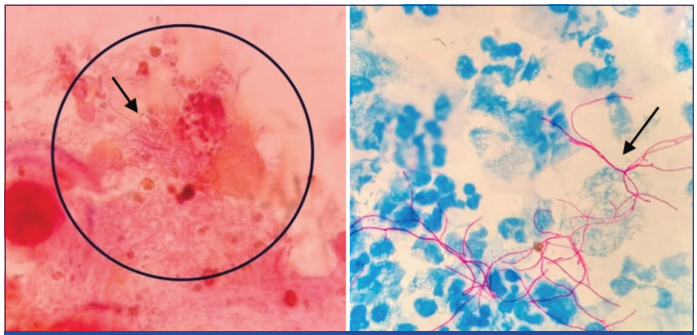
CASE REPORT

A 37-year-old man presented with a five-day history of high-grade fever, productive cough, and weight loss. He was a known case of systemic hypertension and chronic kidney disease, having received a live-related renal transplant a year ago. For this, he was on immunosuppressive therapy with methylprednisolone and tacrolimus. Physical examination revealed a fever of 101.2°F, and auscultation of the chest revealed bilateral coarse lower zone crepitations. Initial investigations showed microcytic hypochromic anaemia (haemoglobin 6.2 g/dL), leukopenia (1710 cells/cu.mm), and elevated renal parameters (serum creatinine 2.8 mg/dL, BUN 52 mg/dL). A chest X-ray indicated right lower zone opacity [Table/Fig-1].



[Table/Fig-1]: Chest radiography image showing opacity in right lower zone.

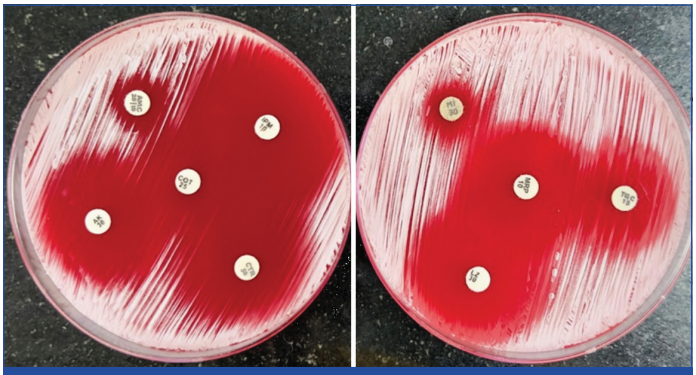
A provisional diagnosis of pulmonary tuberculosis was considered based on the chest X-ray findings. Video bronchoscopy revealed thick mucoid secretions in the bilateral lower lobes, which were sent for microscopy and culture. Gram stain and 1% modified AFB staining were performed on the bronchial secretions. The Gram stain showed a moderate number of inflammatory cells along with filamentous, branching, gram-positive bacilli, and 1% modified AFB staining confirmed the presence of acid-fast filamentous bacilli [Table/Fig-2], suggestive of *Nocardia* spp. Routine AFB staining and potassium hydroxide fungal mounts were negative. Culture on blood agar grew chalky white colonies [Table/Fig-3], which produced catalase and hydrolysed urea. These colonies were identified by Matrix Assisted Laser Desorption Ionisation Time-Of-Flight (MALDI ToF-MS) as *Nocardia cyriacigeorgica*. Susceptibility testing according to the Central Laboratory Standards Institute



[Table/Fig-2]: Gram stain showing inflammatory cells and filamentous gram-positive bacilli with branching on 100x magnification (left); Modified Acid-Fast Bacilli (AFB) in 100x magnification.

[Table/Fig-3]: Few chalky white colonies on 5% sheep blood agar after 72 hours of incubation (left) and subculture of colonies (right).

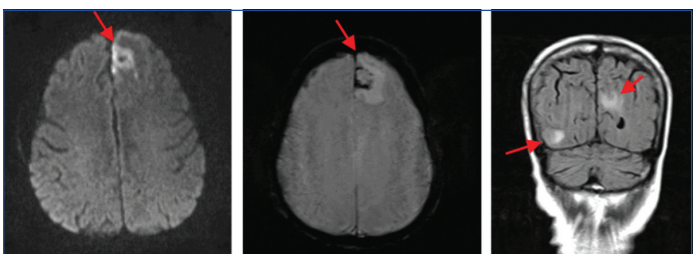
(CLSI) guidelines [1] showed susceptibility to ceftriaxone, amikacin, cotrimoxazole, linezolid, and imipenem, but resistance to amoxicillin-clavulanic acid [Table/Fig-4].



[Table/Fig-4]: Antibiotic susceptibility testing by disc diffusion method.

The patient was treated with oral cotrimoxazole (Sulfamethoxazole 800 mg+Trimethoprim 160 mg) twice daily and intravenous imipenem 500 mg three times daily during the 14 days of hospitalisation. He was also given a single dose of oral linezolid 600 mg on the first day of hospitalisation, which was stopped considering his renal parameters. He received two units of packed red blood cell transfusion for anaemia and was monitored closely for renal function. After 14 days of rigorous treatment, he improved significantly and was discharged with instructions to continue cotrimoxazole and imipenem therapy for two more weeks. However, the patient did not adhere to the antibiotics after discharge.

Ten days after discharge, the patient presented with multiple episodes of seizures and altered sensorium with a Glasgow Coma Scale (GCS) score of 6/15, a high-grade fever, hypotension, and reduced renal output. Magnetic resonance imaging of the brain revealed right frontal and intra-axial lesions with perilesional oedema, suggestive of cerebral abscess [Table/Fig-5]. He was diagnosed with cerebral nocardiosis and was treated with a multidrug regimen consisting of tablet cotrimoxazole 160+800 mg twice daily, injection imipenem 500 mg three times daily, and injection ceftriaxone 1 g twice daily. Unfortunately, he deteriorated over the subsequent hours. The patient progressed to septic shock. Blood cultures did not grow any organism, and within 48 hours, he succumbed despite resuscitation efforts.



[Table/Fig-5]: Magnetic resonance imaging of brain showing intra-axial lesions due to dissemination of infection; arrows point at well-defined, ring-enhancing lesions with perilesional oedema suggestive of abscess due to dissemination of infection from lungs.

DISCUSSION

Genus *Nocardia* comprises aerobic actinomycetes that are gram-positive, filamentous bacilli with a branching and beaded appearance, exhibiting weak acid-fast properties. *Nocardia* species are ubiquitously found in the environment, and infections are often underdiagnosed [2]. Nocardiosis is sporadic in nature, with the pulmonary form being the most common presentation. It clinically and radiologically mimics pulmonary tuberculosis, resulting in an increased likelihood of misdiagnosis [2]. Risk factors such as long-term steroid and immunosuppressant usage, as well as Human Immunodeficiency Virus (HIV) infection, can lead to severe forms of *Nocardia* infection. Currently, there are about 100 identified species of *Nocardia*, more than 50 of which are clinically significant, with reports published from around the globe [2,3].

N. cyriacigeorgica was first identified in a patient with chronic bronchitis in 2001 [4] and has since been reported in Canada, Greece, Turkey, Thailand, and India. This organism has been associated with various manifestations, including pulmonary lesions, cellulitis following dental extraction, bacteraemia, brain abscesses, lesions in solid organ recipients, endophthalmitis, and scleral buckle injuries [5-7]. These manifestations are related to infections or iatrogenic immunosuppression. *N. cyriacigeorgica* commonly disseminates following pulmonary manifestations [8]. A comprehensive 11-year retrospective study from Taiwan revealed that the lungs are the most common site of involvement, followed by the skin and soft tissue. Additionally, the study found that one-third of the population died within three months [9].

Pulmonary and disseminated nocardiosis are common in patients with compromised cell-mediated immunity and those receiving immunosuppressive therapy, while cutaneous infections can occur even in immunocompetent individuals. In this patient's case, the development of opportunistic pulmonary nocardiosis can be attributed to the immunosuppressive therapy involving steroids and a calcineurin inhibitor. Pulmonary nocardiosis typically presents with non specific symptoms that overlap with conditions such as tuberculosis and fungal infections, primarily caused by *Aspergillus* species, making diagnosis challenging [10]. In a country like India, where tuberculosis is endemic, this type of clinical presentation must be carefully addressed, especially in the immunocompromised population.

The microbiological diagnosis of *Nocardia* poses challenges due to the slow growth of the bacteria from respiratory specimens. In present case, growth on enriched medium was observed only after 72 hours of incubation. Additionally, the growth of *Nocardia* colonies may be obscured by the normal flora present in respiratory specimens [3]. Extended incubation of cultures from respiratory specimens of patients with a clinical suspicion of nocardiosis may be beneficial. Advancements in isolation techniques and laboratory diagnostics have significantly contributed to the increased detection of various *Nocardia* species. Laboratory identification of *Nocardia* species was originally based on their ability to utilise specific sugars and decompose substrates. While there are relatively few standardised biochemical tests available, techniques such as 16S rRNA PCR and sequencing, hsp65 sequencing, DNA hybridisation, and MALDI-TOF MS have now established a more accurate classification [11].

Antimicrobial susceptibility and resistance patterns vary among *Nocardia* species. *N. brasiliensis, N. abscessus*, and *N. farcinica* are intrinsically resistant to imipenem, while *N. cyriacigeorgica* is resistant to ciprofloxacin and clarithromycin. Therefore, species identification through conventional biochemical tests, automated identification methods, or sequencing is essential for choosing an effective antibiotic therapy [1,2]. While sulfonamides were the preferred antimicrobials earlier, the current treatment protocol usually consists of cotrimoxazole in combination with ceftriaxone, amikacin, or imipenem [10]. *N. cyriacigeorgica* is usually susceptible

Report/Study	Place and year of publication	Clinical diagnosis	Risk factor(s) present	Treatment given	Outcome
Namnyak S et al., [5]	United Kingdom, 2011	Pneumonia and bacteraemia	Renal transplant recipient on oral immunosuppression	Injection imipenem, high dose oral cotrimoxazole	Succumbed
Manoharan H et al., [12]	Chennai, India, 2019	Bilateral bronchiectasis with respiratory failure and pulmonary tuberculosis	Pulmonary tuberculosis on remission	Injection imipenem, oral cotrimoxazole, followed by only oral cotrimoxazole for six months	Recovered
Bora A et al., [6]	Rajasthan, India, 2019	Intraoral cellulitis with discharging sinuses	Dental extraction by an unauthorised medical practitioner	Surgical incision and drainage, oral cotrimoxazole for four months	Recovered
Dutta S and Ray U [3]	Kolkata, India, 2020	Necrotising pneumonia with right sided pleural effusion	Renal transplant recipient on triple drug immunosuppression	Double strength oral cotrimoxazole TID for six months	Recovered
Gabay S et al., [13]	Israel, 2022	Brain abscess	Low dose steroids for hormonal remission of prostrate carcinoma	Parietal craniotomy with drainage, injection meropenem and cotrimoxazole	Recovered
Kashyap H et al., [7]	Chennai, India, 2024	Scleral buckle infection	Scleral buckle surgery for retinal detachment	Buckle explant excision, fortified amikacin 2.5% eye drops for 8 times a day and oral cotrimoxazole BD for one week	Recovered
Present study	Chennai, India, 2024	Pneumonia and cerebral abscess	Renal transplant recipient on immunosuppressive therapy	Oral cotrimoxazole along IV imipenem for two weeks	Succumbed

[Table/Fig-6]: Reports on a few varied presentations of *Nocardia cyriacigeorgica* in patients with a co-existing risk factor(s); (Details about the dosing of prescribed antibiotics have been added wherever details were available) [3,5-7,12,13].

to cephalosporins, imipenem, amikacin, linezolid, and cotrimoxazole but resistant to penicillin, amoxicillin-clavulanic acid, clarithromycin, and ciprofloxacin [1]. Cotrimoxazole is the cornerstone of treatment for various clinical forms of nocardiosis, as most species are susceptible to this drug. Literature states that the outcome after antibiotic treatment for nocardiosis is excellent with combination therapy involving multiple drugs. The duration of treatment is crucial to prevent relapse of infection. As *Nocardia* replicates slowly and may remain as cryptic intracellular organisms, these often tend to relapse [2]. Hence, extended antimicrobial therapy lasting from a few weeks to several months is necessary. The treatment duration for pulmonary or systemic infections varies from two weeks to up to six months, and may even extend up to 12 months in cases of cerebral nocardiosis [2,3]. Clinical improvement can be assessed after two weeks of treatment initiation, and surgical intervention is indicated in appropriate cases. Successful clinical outcomes with no relapses have been reported in several cases of *N. cyriacigeorgica* infections when patients were treated with a strict combination regimen over an extended duration [Table/Fig-6] [3,5-7,12,13]. However, careful monitoring of antibiotic-related toxicity is advised.

Poor prognosis is observed either during a delay in diagnosis or when treatment is deferred or not adhered to. The outcome depends largely on the extent of the infection and patient factors [2,3]. According to a report from the USA, mortality rates for nocardiosis can reach up to 25% for pulmonary manifestations and up to 100% in cases involving the central nervous system [14]. An Indian report stated a mortality rate of 31.25% for pulmonary and dermal nocardiosis, with a 100% mortality rate in cerebral nocardiosis [15]. Previously published reports on varied presentations of *N. cyriacigeorgica* from India have shown good recovery with almost no relapses, thanks to the prompt identification of the causative organism, an effective antibiotic regimen, and meticulous follow-up of the patient [Table/Fig-6]. Reports published from India over the last decade have mostly indicated that patients have completely recovered after adhering to treatment [Table/Fig-6]. In present case, the unfavourable outcome may be attributed to the patient's non adherence to treatment and existing co-morbid conditions, which heightened the risk of dissemination within days. Accurate identification, prompt initiation, and maintenance of appropriate treatment will greatly reduce *Nocardia*-related mortality.

CONCLUSION(S)

Nocardia species are particularly significant in cases associated with immunosuppression due to their non specific presentation, which mimics tuberculosis. Therefore, accurate identification is essential in regions where tuberculosis is endemic. Advances in laboratory diagnostics, such as MALDI-TOF MS and gene sequencing, have aided in the precise identification and classification of these species. Antimicrobial treatment for any form of nocardiosis necessitates a multidrug regimen, usually including cotrimoxazole and imipenem, for an adequate duration based on the severity of the infection. Successful outcomes depend on early diagnosis, prompt initiation, and strict adherence to treatment protocols, as delays or non adherence can result in poor prognosis.

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