

A Rare Case Report of Disseminated *Nocardia farcinica* Granulomatous Hepatitis and Clinical Management Experience

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Background: Nocardiosis is primarily an opportunistic infection affecting immunocompromised individuals, with a predilection for the lungs, brain, or skin in those with compromised immune function. Granulomatous hepatitis caused by *Nocardia* is a rare clinical manifestation. This study aims to provide a systematic overview of the clinical features of Nocardiosis caused by *Nocardia farcinica*, enhancing our understanding of this disease.

Methods: We report a case of a 75-year-old male with no underlying diseases presenting with a history of “recurrent fever for more than 4 months”, along with fatigue, poor appetite, and pleural and abdominal effusion. Despite treatment at multiple hospitals, the patient showed little improvement. Chest CT revealed chronic inflammation, small nodules, bilateral pleural effusion, and pleural thickening. Abdominal CT indicated multiple low-density lesions in the liver, multiple small calcifications, and abdominal effusion.

Results: Liver biopsy suggested inflammatory changes, with focal granuloma formation. Metagenomic next-generation sequencing (mNGS) of liver tissue indicated *Nocardia farcinica*, leading to the final diagnosis of disseminated *Nocardia farcinica* granulomatous hepatitis.

Conclusion: *Nocardia* infection is a rare disease primarily observed in immunocompromised patients but can also occur in those with normal immune function. The clinical and radiological features lack specificity; however, the utilization of mNGS technology enables rapid identification of the pathogenic microorganism. *Nocardia farcinica* is generally susceptible to sulfonamide drugs and amikacin, offering viable treatment options.

Keywords: *nocardia farcinica*, granulomatous hepatitis, disseminated infection, mNGS Technology, TMP-SMX

Introduction

Nocardiosis, caused by members of the *Nocardia* genus, is a rare yet potentially life-threatening infectious disease. It primarily occurs in individuals with compromised or suppressed immune systems but can also infect those with normal immune function.¹ The pathogen primarily enters through inhalation via the respiratory tract or direct invasion through the skin and soft tissues. Common sites of infection include the lungs, skin, and central nervous system. Disseminated infections involving multiple organ systems are less frequent but can pose a life-threatening risk.² *Nocardia* species as well as the invasiveness of each one may depend on geographic variations.³ *Nocardia farcinica* constitutes 24.5% of all *Nocardia* infections, and it is more prone to causing disseminated infections with a higher mortality rate.⁴ *Nocardia*, as a pathogen affecting humans, receives relatively less attention. Due to challenges in its discovery and diagnosis, there is often a delay in treatment, leading to unfavorable prognoses.⁴ This study reports a case of an immunocompetent patient who developed granulomatous hepatitis due to *Nocardia farcinica* infection.

Case Report

Patient, male, 75 years old. The patient began experiencing intermittent fever in April 2023, with fever occurring 1–2 times per week and reaching a peak temperature of 38°C. He presented with fatigue and poor appetite, without cough or sputum symptoms. In July 2023, the fever became more frequent, with a peak temperature of 39.1°C. Hospital examinations revealed decreased white blood cell count, elevated erythrocyte sedimentation rate, decreased albumin, reduced white cell ratio, blood and protein in urine. Blood culture detected *Staphylococcus saprophyticus*, while sputum and urine cultures were negative. Chest CT scans showed chronic inflammation, small nodules in both lungs, bilateral pleural effusion, and pleural thickening (Figure 1). Abdominal CT indicated multiple low-density lesions in the liver and spleen, with multiple small calcifications in both organs (Figure 2). A cyst was observed in the right kidney, along with abdominal effusion. Consider the presence of *Staphylococcus saprophyticus* infection. The patient sought treatment in multiple hospitals and received ineffective antimicrobial therapy including cephalosporins, piperacillin-tazobactam, and meropenem. These treatments are not effective. In August 2023, a liver biopsy was performed, revealing focal granuloma formation suggestive of inflammatory lesions. Tuberculosis infection T-cell testing was positive, leading to the initiation of empirical anti-tuberculosis treatment with isoniazid, rifampicin, ethambutol, and pyrazinamide. However, the response was inadequate. During this time the patient developed a mild cough and sputum, and we retained a sputum culture which was negative. After nebulization, the cough and sputum disappeared. In September 2023, metagenomic next-generation sequencing (mNGS) of liver tissue identified the presence of *Nocardia farcinica*. The treatment was modified to include sulfamethoxazole-trimethoprim, amikacin, and meropenem, resulting in effective control of fever symptoms. Oral sulfamethoxazole-trimethoprim was planned for a 6-month duration, but due to a systemic rash during oral administration, minocycline was substituted. Follow-up has not revealed recurrence of fever symptoms.



Figure 1 Chest CT: Chronic inflammation in both lungs, nodules visible in both lungs (as indicated by the blue arrows).

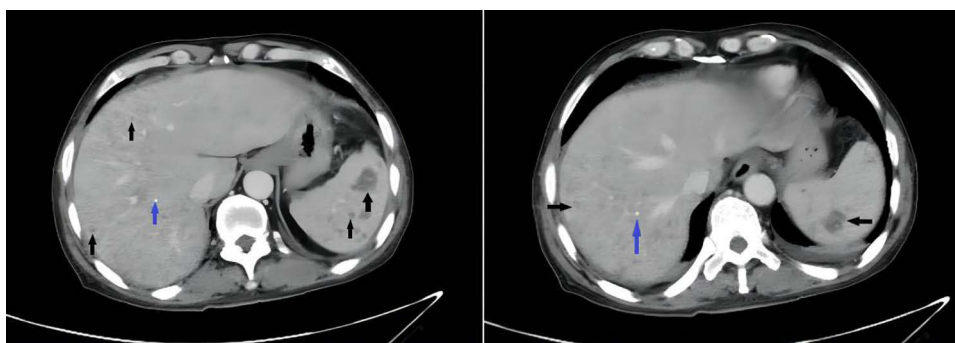


Figure 2 Abdominal CT reveals multiple low-density lesions in the liver and spleen (black arrows), along with multiple small calcifications (blue arrows).

Discussion

Nocardia belongs to the bacterial domain, Actinobacteria phylum, Actinomycetales order, Nocardiaceae family. It is a group of aerobic, Gram-positive bacteria with positive urease and catalase activity. These rod-shaped bacteria can form branched filaments, are partially acid-fast, and are commonly found in soil, dust, and decomposing vegetation.⁵ In 1988, French veterinarian Edmond Nocard isolated *Nocardia* from cattle affected by “bovine farcy”. In 1989, it was officially named by Trevisan. That same year, Eppinger reported the first case of natural human infection.⁶ The latest research has confirmed 54 different species of *Nocardia* associated with human infections, placing them prominently among the known 119 species.^{7,8} Among these, the four main pathogenic species to humans are: *Nocardia asteroides*, *Nocardia farcinica*, *Nocardia brasiliensis*, and *Nocardia otitidiscaviarum*.⁹ *Nocardia farcinica* is a bacterial pathogen characterized by a clinically insidious onset, intense tissue damage, and a tendency for recurrence.¹⁰ In a study that surveyed *Nocardia* species in China, it was found that the most commonly isolated strain is *Nocardia farcinica*, accounting for up to 29.9%.¹¹

Nocardia is not a part of the normal human flora; it is an exogenous pathogen causing opportunistic infections in humans.¹² The risk of *Nocardia* infection is elevated in individuals with compromised immune systems, such as those undergoing immunosuppressive therapy, receiving corticosteroid treatment, undergoing anti-tumor necrosis factor monoclonal antibody therapy, or having HIV infection.¹³ Susceptibility to *Nocardia* infection is also increased in individuals with malignant tumors, Cushing’s syndrome, chronic granulomatous diseases, diabetes, abnormal gammaglobulinemia, chronic pulmonary diseases, and solid organ transplants.¹⁴ In some cases, *Nocardia* infection occurs in individuals with normal immune function and without underlying primary diseases.¹⁵ In the cases studied, the patient was immunocompetent with no underlying diseases, except for advanced age.

Clinical manifestations of Nocardiosis lack specificity, and the diverse locations of infection can result in various symptoms.¹⁶ *Nocardia* species typically enter the human body through the respiratory, digestive, or damaged skin, causing localized infections. Although it can spread through the bloodstream to multiple organs, the most common route is respiratory, resulting in symptoms such as fever, cough, sputum production, hemoptysis, chest pain, and pleural effusion.¹⁷ Common CT manifestations of *Nocardia* pneumonia include pulmonary nodules, diffuse or focal lung infiltrates, lung abscesses, and pleural effusion.¹⁸ Immunocompromised individuals are more prone to extrapulmonary dissemination of *Nocardia*, spreading to the liver, central nervous system, subcutaneous tissues, and other locations.¹⁹ Infections caused by *Nocardia* leading to central nervous system damage typically result in the formation of one or more masses in the brain. The primary symptoms include increased intracranial pressure, such as headaches, nausea, vomiting, lethargy, and, in some cases, seizures.^{20,21} Additionally, literature reports indicate that *Nocardia* may also cause conditions such as exudative choroiditis, retinal abscess, iridocyclitis, keratitis, peritonitis, arthritis, and infective endocarditis.^{22–24} Clinical reports on *Nocardia*-induced liver infections are relatively scarce, with manifestations typically involving the formation of hepatic granulomas and liver abscesses.^{25,26} In most cases, *Nocardia* infections are extremely rare, but should be considered when results for more common causes are negative.²⁷ Nocardiosis shares similarities in most clinical symptoms and radiological presentations with tuberculosis and non-tuberculous mycobacterial infections. This similarity can lead to misdiagnosis or missed diagnosis.²⁸ Reviewing the patient’s medical history in this case, the initial site of *Nocardia* infection was considered to be the lungs; however, the patient did not exhibit significant cough or sputum symptoms, presenting only with fever. The patient lacked significant cough and sputum symptoms early in the course of the disease, so sputum culture tests were not performed at the outside hospital, which may have limited the ability to detect *Nocardia* at an early stage. Later in the course of the disease, the patient developed mild cough and sputum symptoms and we performed a well-established sputum culture test which was negative. This may have been due to some reason for not being able to detect the presence of *Nocardia*, such as a low bacterial load or the influence of other factors. As the patient’s cough and sputum symptoms were relieved after nebulization treatment, it resulted in sputum specimens that were difficult to retain. This affected the subsequent sputum culture tests. This lack of prominent respiratory symptoms led to the initial oversight of considering pulmonary *Nocardia* infection, resulting in a complicated treatment course. Subsequently, granulomatous hepatitis was discovered through a liver biopsy, with a positive T-SPOT test. The initial diagnosis had suspected tuberculosis, but the response to anti-tuberculosis treatment was poor. A positive T-SPOT positive result may be due to a previous TB infection. Or the TB bacilli have entered the

body and triggered an immune response, but the patient has not developed active TB disease and may be a latent TB infected individual. Our experience from this case emphasizes that *Nocardia* infections are rare, and if other test results are negative, consideration of this infection is crucial.

Nocardiosis patients typically lack specific symptoms, making diagnosis challenging. Definitive diagnosis often relies on histopathological examination of tissue and/or culture.²⁹ Direct microscopy and bacterial culture remain the primary methods for diagnosing Nocardiosis, with microbial culture from the site of infection serving as the gold standard for confirming the diagnosis.³⁰ The presence of “sulfur granules” in infected tissues and pus is a characteristic feature. Microscopically, these granules consist of branched filaments, with rod-shaped filaments surrounding them. In sputum and cerebrospinal fluid, only Gram-positive branching and rod-shaped bacteria can be observed. It is essential to differentiate from *Mycobacterium tuberculosis*.³¹ mNGS is a highly sensitive and high-throughput detection method. It identifies the presence of microorganisms and their relative proportions by aligning all nucleic acids in a sample with a reference genome.³² Compared to traditional culture methods, mNGS has a shorter detection period and higher sensitivity, especially for samples that may go undetected through traditional culture.^{33,34} However, the main drawback of mNGS is its high cost, which may be a burden for some patients.³⁵

Sulfamethoxazole-trimethoprim (SMZ-TMP) has consistently been the first-choice medication for treating *Nocardia* infections.³⁶ As a sulfonamide drug, sulfamethoxazole-trimethoprim (SMZ-TMP) inhibits bacterial synthesis of dihydrofolate, thereby preventing bacterial growth and reproduction. In addition to SMZ-TMP, other antibiotics are also considered effective treatment options, including amikacin, imipenem, third-generation cephalosporins, and linezolid.³⁷ Once diagnosed with Nocardiosis, long-term treatment is typically required. The duration of treatment often exceeds six months and depends on various factors, including the severity of the disease, the patient’s immune status, clinical course, and the organ systems affected by the infection.

Conclusion

Nocardia is a type of Gram-negative rod-shaped bacterium commonly found in environments such as soil, water sources, and plants. Despite its widespread presence in nature, instances of causing infections in humans are relatively rare. Typically, *Nocardia* infections primarily involve the lungs, skin, and brain. However, this study indicates that the liver could also be another potential site of infection. Clinically, it is often confused with tuberculosis. In diagnosing *Nocardia* infections, mNGS can confirm the presence of infection by analyzing the genomic sequences of *Nocardia* in patient tissue samples (such as blood, tissues, and fluids). Sulfamethoxazole-trimethoprim (SMZ-TMP) is the preferred treatment, requiring an adequate duration of therapy.

Data Sharing Statement

All data and materials of this article are included in the manuscript.

Ethics Approval and Consent to Participate

All methods in this study were performed by the relevant guidelines and regulations of the Declaration of Helsinki and were approved by the Ethics Committee of the Anhui Provincial Hospital of Integrated Traditional Chinese and Western Medicine.

Consent for Publication

This study obtained written informed consent from the patients themselves. A copy of the written consent can be provided upon request.

Author Contributions

All authors made substantial contributions to the development and execution of the study, including the design, data acquisition, analysis, and interpretation. The authors participated in the drafting, revision, and critical review of the article and gave their final approval for publication. They are accountable for all aspects of the work and have agreed on the submission to the specified journal.

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Disclosure

The authors report no conflicts of interest in this work.

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