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CASE REPORT

Elusive Diagnosis of Recurrent Subcutaneous Emphysema: *Nocardia farcinica* Infection in an Immunocompetent Female Patient

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Abstract: This case report describes an immunocompetent female with recurrent subcutaneous emphysema and refractory soft tissue infections involving multiple non-contiguous sites—bilateral breasts, chest wall, and upper limb—over seven years, consistent with disseminated nocardiosis. Initial presentations mimicked bacterial mastitis, with localized swelling, erythema, crepitus, and elevated inflammatory markers. Despite repeated incision and drainage procedures, antibiotic therapies, and bilateral mastectomies, symptoms recurred persistently. Conventional microbial cultures repeatedly failed to identify a pathogen, while metagenomic next-generation sequencing (mNGS) of a late-stage chest wall lesion ultimately revealed *Nocardia farcinica*, an opportunistic actinomycete with a known propensity for systemic dissemination even in immunocompetent hosts. The patient's atypical clinical course—marked by multifocal gas-forming soft tissue necrosis, chronic recurrence, and resistance to empiric treatments—underscores the diagnostic challenges posed by fastidious pathogens like *Nocardia*. Key lessons include the utility of mNGS in identifying culture-elusive organisms, the importance of considering nocardiosis in refractory subcutaneous infections regardless of immune status, and the necessity of prolonged, targeted antimicrobial regimens (eg, sulfonamides) combined with surgical intervention. This case highlights evolving paradigms in managing complex disseminated infections through advanced genomic diagnostics and multidisciplinary approaches.

Keywords: *Nocardia farcinica*, subcutaneous emphysema, refractory soft tissue infection, metagenomic next-generation sequencing, mNGS, immunocompetent host

Introduction

Nocardia farcinica is an opportunistic pathogen that commonly causes life-threatening disseminated infections in immunocompromised individuals.[1,2] While the precise incidence of this pathogen remains to be fully determined, infections in immunocompetent hosts are regarded as uncommon and are frequently linked to disseminated clinical presentations.[1,3,4] Cutaneous or subcutaneous *Nocardiosis* is a highly uncommon condition among immunocompetent individuals, frequently resulting from minor traumatic events, and presents considerable challenges in diagnosis.[5] However, cases documented in the literature presenting with localized subcutaneous manifestations—such as recurrent subcutaneous emphysema and pain—in the absence of pulmonary or central nervous system involvement are exceptionally rare.[6,7] This case report presents a patient with no prior history of immunodeficiency who exhibited recurrent non-traumatic subcutaneous emphysema and pain in the absence of disseminated disease, underscoring the importance of maintaining heightened clinical suspicion for such atypical infections.[6]

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Case Presentation

Clinical Features

A 38-year-old Chinese female was admitted to the hospital with complaints of initial left breast swelling and pain, which developed subsequent to an upper respiratory tract infection and was later found to be part of a disseminated infection. Upon admission, clinical examination revealed localized swelling and erythema of the left breast, accompanied by tenderness upon palpation and a characteristic crepitus suggestive of subcutaneous emphysema (Figure 1A and B,

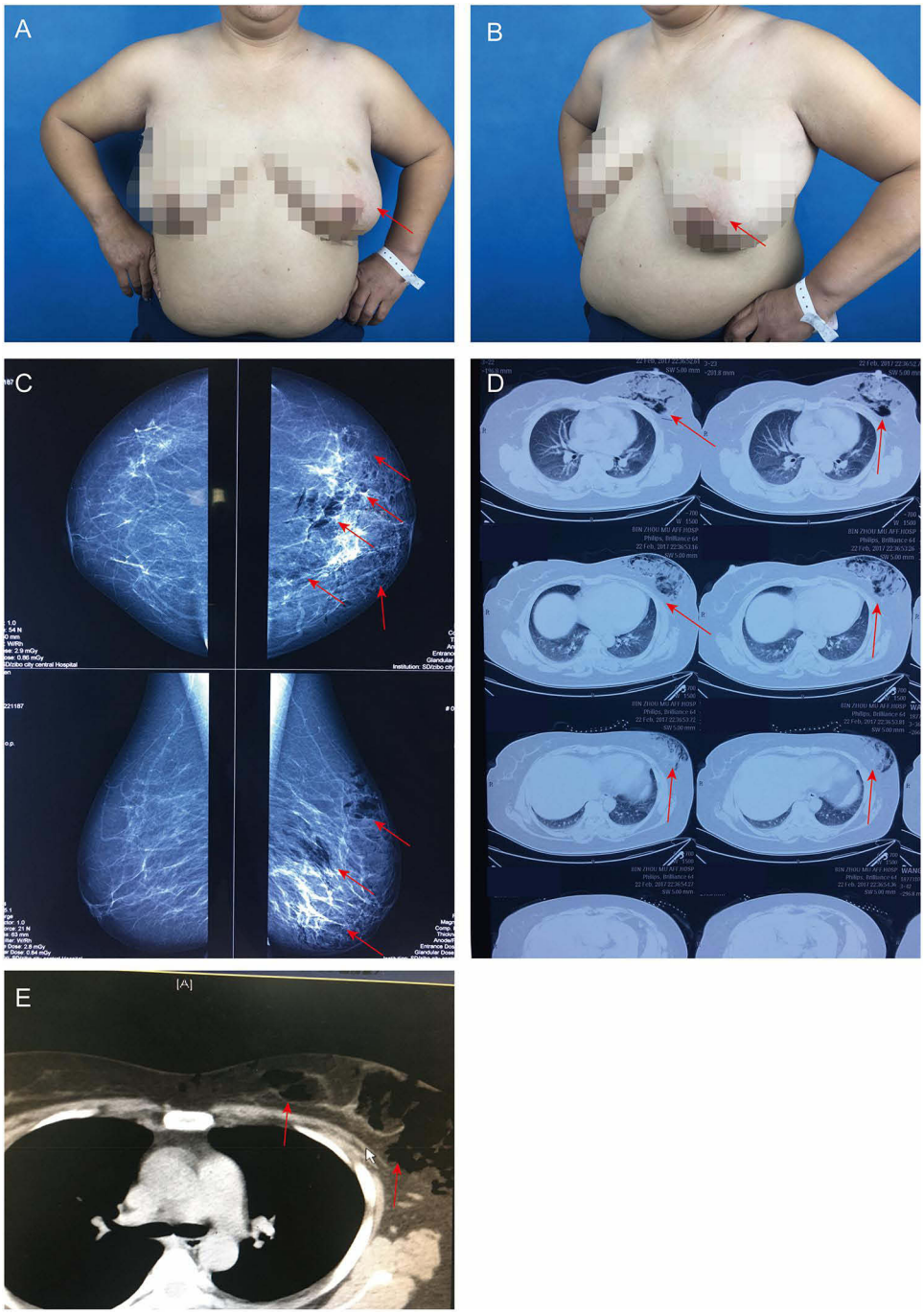

Figure 1 Preoperative clinical signs and imaging findings of the patient. (**A** and **B**) clinical photograph showing localized swelling and erythema of the left breast and tenderness on palpation; (**C**) mammographic view of the left breast demonstrating multiple radiolucent gas shadows, consistent with gas accumulation, and diffuse increased density in the mammary tissue layer, indicative of inflammatory changes; (**D** and **E**) computed tomography revealed a gas-density opacity in the left mammary region. Red arrows point to the locations of both visible lesions and radiographic anomalies.

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Supplementary video). Moreover, physical examination revealed no pathological breath sounds or cardiac abnormalities, and the abdomen was noted to be soft without tenderness or guarding. The patient's temperature was normal, and she had no history of hypertension or diabetes, nor history of long-term drug use. Abnormal elevation of WBC ($12.5x10^9$/L), Neutrophils ($9.2x10^9$/L), C-reactive protein (CRP) (17.90 mg/L) and erythrocyte sedimentation rate (ESR) (87 mm/h) were indicated by blood routine examination (Table 1).

Imaging Examination

Mammography demonstrates the presence of multiple radiolucent gas shadows within the left breast, along with diffuse increased density in the mammary tissue layer, consistent with inflammatory changes (Figure 1C). Computed tomography revealed a gas-density opacity in the left mammary region (Figure 1D and E).

Therapeutic Process

The patient reported severe pain that was unresponsive to initial empirical antibiotic therapy. Following confirmation of surgical eligibility through exclusion of contraindications, incision and drainage of the left breast were subsequently performed (Figure 2A). No significant organic abnormalities were identified in the breast intraoperatively, and there was no evidence of infection or abscess formation (Figure 2B). Postoperative bacterial culture confirmed the presence of Staphylococcus epidermidis. The patient demonstrated clinical improvement following targeted antimicrobial therapy and was subsequently discharged in stable condition.

However, following discharge, the patient experienced recurrent episodes of subcutaneous emphysema and infection in the left breast. Despite repeated interventions including incision and drainage as well as antibiotic administration, the clinical response remained suboptimal. The patient complained of unbearable pain. Following a thorough discussion and respecting the patient's autonomous decision, a simple mastectomy was performed on the left breast. Postoperative pathological analysis revealed partial disruption of the mammary lobular architecture, characterized by localized necrosis, hyperplasia of granulation tissue, and a marked infiltration of multinucleated giant cells (Figure 2C). Regrettably, the pain relief persisted for only three months. Subsequently, similar symptoms recurred in the patient's right breast, necessitating a second mastectomy on the contralateral side (Figure 2D).

Over the subsequent seven-year period, the patient experienced recurrent episodes of subcutaneous emphysema complicated by infection involving the left upper limb (Figure 2E and F), left chest wall, and adjacent anatomical regions. Despite repeated

Table 1 Clinical and Laboratory Indicators of the Patient

Laboratory Indicators/Clinical Indicators	Measurements	Normal Interval
WBC	**12.5x10⁹/L**	3.5–9.5x10⁹/L
Lymphocytes	2.8x10⁹/L	1.1–3.2x10⁹/L
Monocytes	0.4x10⁹/L	0.1–0.6x10⁹/L
Neutrophils	**9.2x10⁹/L**	1.8–6.3x109/L
Eosinophils	0.04x10⁹/L	0.02–0.52x10⁹/L
Basophils	0.03x10⁹ /L	0-0.06x10⁹/L
RBC	4.3x10¹² /L	3.8–5.1x10¹² /L
Hemoglobin	137 g/L	115–150 g/L
Platelets	337x10⁹ /L	125–350x10⁹ /L
CRP	**17.90 mg/L**	0–6 mg/L
ESR	**87 mm/h**	0–20 mm/h

Notes: Bold text indicates the abnormal test results.

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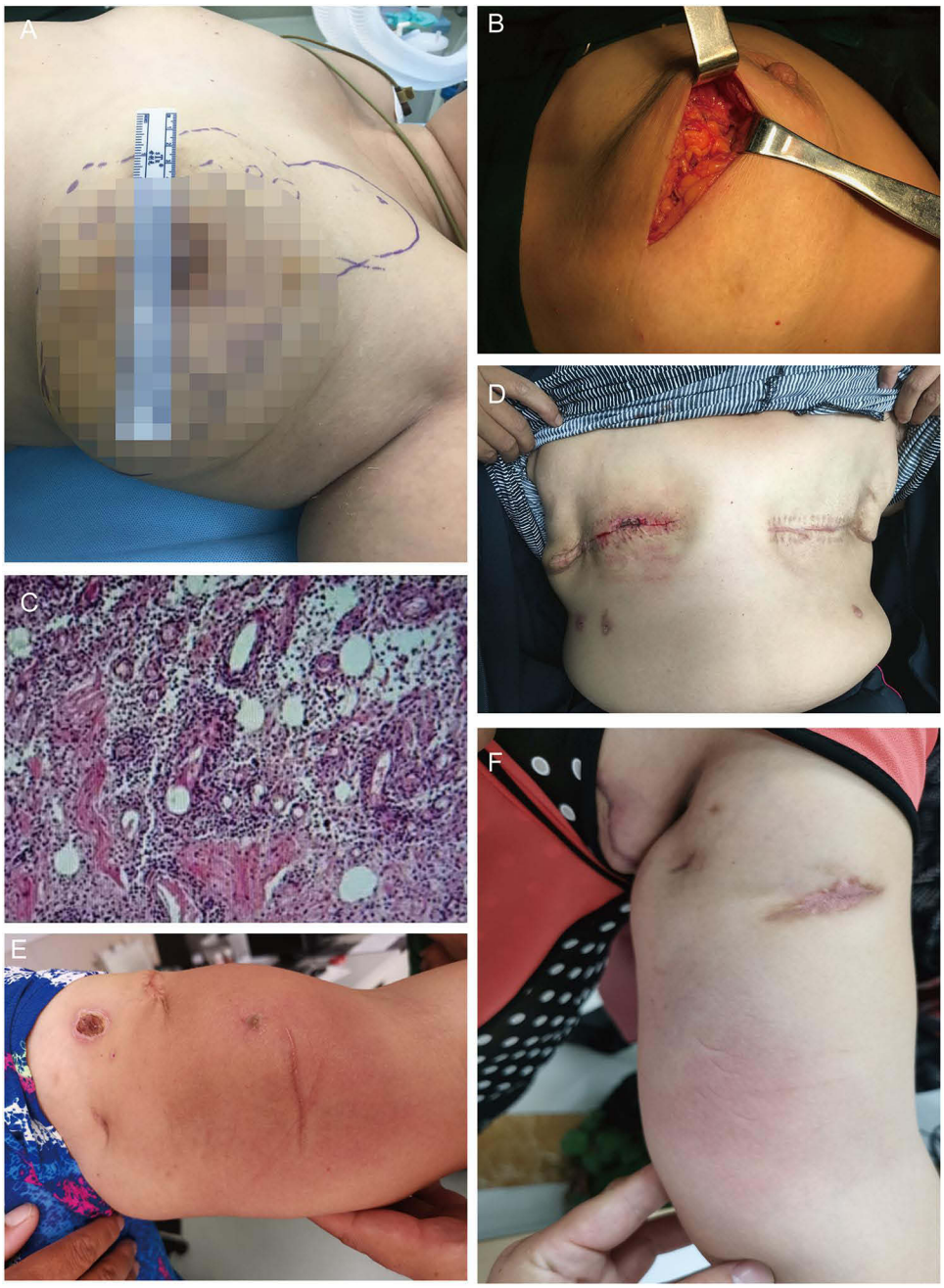

Figure 2 The patient's therapeutic course. (**A**) preoperative preparation; (**B**) intraoperative examination of the breast demonstrated no organic abnormalities, infection, or abscess formation; (**C**) HE-stained histopathological image of the specimen obtained following unilateral mastectomy; (**D**) postoperative images following bilateral mastectomy; (**E** and **F**) clinical images demonstrating subcutaneous emphysema and infection affecting the left upper limb.

interventions, including incision and drainage, transient clinical improvement was observed, followed by disease recurrence. It is noteworthy that throughout the observation period, repeated microbiological cultures were conducted using blood samples, tissue homogenates, and lavage fluids; however, no specific pathogenic bacterial strains were identified. The patient consulted at multiple tertiary medical institutions but did not receive any effective long-term therapeutic interventions.

More than 20 days prior, the patient was readmitted to the hospital with left-sided chest swelling, subcutaneous emphysema, and severe pain following an episode of upper respiratory tract infection. Physical examination revealed no evidence of skin ulceration, sinus tracts, or cutaneous defects on the chest wall. A localized area of erythema and swelling measuring approximately 10 cm x 10 cm was noted in the left thoracic region adjacent to the axilla (Figure 3A). Palpation

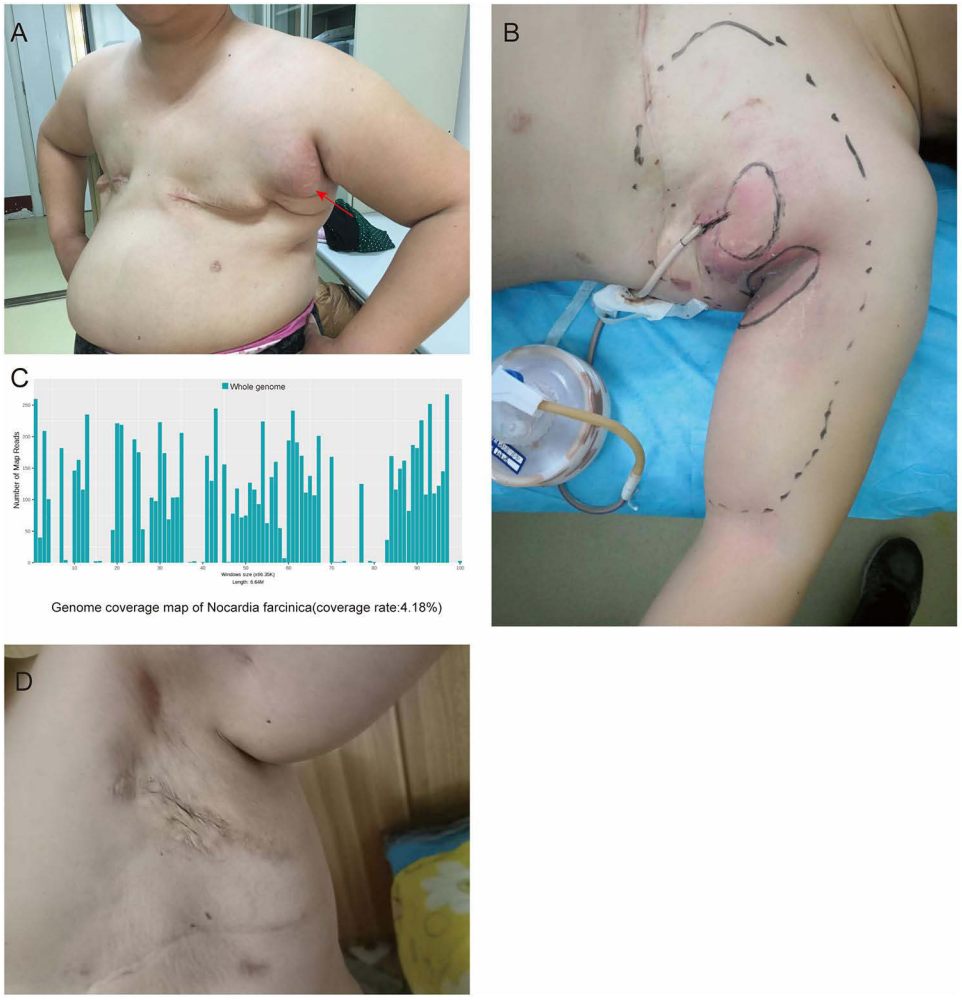

Figure 3 The most recent treatment course. (**A**) Localized erythema and swelling (approximately 10×10 cm) observed in the left thorax adjacent to the axillary region; (**B**) postoperative photographic documentation following resection and drainage of chest wall lesions; (**C**) genome coverage map of Nocardia farcinica (coverage rate: 4.18%); (**D**) No evidence of recurrence was detected during the 12-month postoperative follow-up period. Red arrows point to the locations of visible lesions.

revealed increased local skin temperature, subcutaneous crepitus, and marked tenderness. No palpable enlarged lymph nodes were detected in either axilla. Following completion of preoperative preparations, the patient underwent surgical resection of the chest wall lesion (Figure 3B). This time, a biopsy was obtained for the purpose of obtaining tissue for metagenomic Next Generation Sequencing(mNGS) and subsequent identification of the bacterial species present.

Etiological Examination

Specimen handling and the identification procedures were followed standard laboratory protocols. The mNGS analysis of the tissue biopsy indicated the presence of *Nocardia* infection, specifically *Nocardia farcinica*(sequence number: 21885, confidence coefficient:99%) (Figure 3C). The patient has no underlying medical conditions associated with immunosuppression, and tested negative for human immunodeficiency virus (HIV) infection. Based on the aforementioned clinical findings, the patient was diagnosed with primary cutaneous *Nocardia* resulting from *Nocardia farcinica* infection. We did not conduct drug sensitivity experiments. Following consultation with the clinical pharmacy department, the patient received compound sulfamethoxazole combined with ceftriaxone for anti-infective therapy as recommended. The patient demonstrated a favorable recovery and was subsequently discharged. A follow-up period exceeding one-year post-discharge revealed no evidence of recurrence (Figure 3D).

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Discussion

Nocardia farcinica is a Gram-positive, partially acid-fast, methamine silver-positive aerobic actinomycete that is infrequently encountered in clinical settings and is commonly recognized as an opportunistic pathogen affecting immunocompromised individuals.[1] *Nocardiosis* remains an uncommon opportunistic infection, but its incidence is anticipated to increase in modern healthcare settings. This trend is driven by rising numbers of individuals with chronic lung diseases or immunocompromising conditions, as identified in epidemiological discussions.[8] Although the susceptibility to infection is relatively low in individuals with intact immune function, accumulating evidence in recent years indicates that this bacterial species is capable of causing disease in immunocompetent hosts, often presenting with uncommon or atypical clinical features.[1,3] This case report describes an exceptionally rare instance of *Nocardia* infection in a patient with no prior history of immunodeficiency. The clinical presentation was predominantly marked by recurrent subcutaneous emphysema and localized pain, in the absence of pulmonary or central nervous system involvement—a phenomenon scarcely documented in the existing literature. Infections caused by *Nocardia farcinica* in immunocompetent individuals are frequently linked to minor traumatic events. As demonstrated in this case, such occurrences suggest that the pathogen may gain direct entry through compromised skin barriers, leading to localized abscess formation or emphysema without necessitating systemic dissemination.[3,5] It is noteworthy that *Nocardia farcinica* exhibits relatively high virulence and demonstrates intrinsic resistance to multiple classes of antibiotics. These characteristics further underscore the critical importance of accurate and timely identification in immunocompetent hosts, as failure to diagnose may result in severe clinical complications.[9,10]

This case is distinguished by its multifocal clinical presentation, with primary involvement of subcutaneous tissue and evidence of dissemination to other sites—a pattern that is consistent with the typical hematogenous spread of *Nocardia* described in the majority of published literature. *Nocardia* is classically known to disseminate via the bloodstream, resulting in multifocal involvement of the lungs, central nervous system, and other systemic organs.[9,10] In this case, even in an immunocompetent patient, the infection manifested as multiple cutaneous lesions with systemic dissemination, including palpable swelling or inflammatory changes, potentially arising from minor traumatic events.[3,7] For example, a prior case report described a 37-year-old immunocompetent male who developed palpable swelling following container-related trauma, a clinical presentation that closely resembles the recurrent subcutaneous emphysema observed in our patient.[3] This localized manifestation may be attributed to the host's preserved immune competence, which effectively limits bacterial dissemination. The lack of systemic symptoms, such as fever or cough, contributes to the diagnostic difficulty, as nonspecific clinical features are frequently mistaken for those of common dermatological infections.[7,11] In addition, subcutaneous emphysema caused by *N. farcinica* infection is extremely rare and may be induced by tissue necrosis or gas production-related mechanisms, which is similar to the pathology of subcutaneous abscesses described in the literature.[7] Therefore, this case underscores the importance of considering *Nocardia farcinica* as a potential etiological agent of rare localized infections, even in immunocompetent individuals, particularly in cases of persistent or recurrent symptoms. Comprehensive microbiological analysis is essential to achieve an accurate diagnosis.[3,11]

Regarding diagnostic and management strategies, this case illustrates the critical importance of prompt recognition and directed therapeutic interventions to prevent progression to disseminated disease. The accurate diagnosis of *Nocardia farcinica* infection depends on microbiological culture combined with molecular methods, such as mNGS sequencing, which are essential for species identification and characterization of multidrug-resistant profiles.[12] Upon diagnosis, prolonged antibiotic therapy constitutes a cornerstone of treatment. Specifically, sulfamethoxazole-based regimens have demonstrated consistent efficacy and must be administered for extended durations—typically several months—to ensure complete microbial eradication.[13,14] Given the organism's propensity for developing resistance to multiple antibiotic classes, including third-generation cephalosporins as documented in several studies, treatment individualization based on antimicrobial susceptibility testing is imperative. Close monitoring of clinical response is also essential to prevent relapse and ensure therapeutic success.[9,15]

Treatment failure in *Nocardiosis* can be attributed to multiple factors, including host immune status, pathogen characteristics, and suboptimal therapeutic strategies. Immunocompromised conditions are a key driver of poor outcomes, as patients with disseminated infections or underlying immunosuppression often experience higher mortality rates despite intensive antibiotic regimens.[16] Additionally, standard therapies may fail when used alone, as seen in a case where deterioration occurred under monotherapy; however, coadministration of adjuvant agents like interferon gamma

substantially improved outcomes, suggesting that immune modulation could play a critical role in refractory infections.[17] Furthermore, susceptibility testing is essential due to variable antibiotic responses, as reliance on empiric treatment without targeted therapy based on species identification and AST results can lead to suboptimal outcomes.[18] Overall, treatment failures are often multifactorial, emphasizing the need for personalized approaches considering host immunology, pathogen susceptibility, and potential adjuvant therapies.

A major limitation of this study is the lack of antimicrobial susceptibility testing, which could have provided crucial insights into the treatment failure observed. Fortunately, the empirical treatment demonstrated favorable therapeutic outcomes. Moreover, while our patient did not exhibit neurological signs, we recognize this as a limitation in our initial evaluation. We did not perform a brain CT based solely on the absence of symptoms; however, literature supports universal brain imaging in disseminated nocardiosis.[19] We acknowledge this oversight in the diagnostic and treatment process and recommend the inclusion of brain CT or MRI scans as part of routine diagnostic protocols for similar cases in future clinical practice.

In summary, this case offers significant insights into rare localized *Nocardia farcinica* infections occurring in immunocompetent hosts. It underscores the necessity of maintaining heightened clinical suspicion in cases presenting with similar manifestations, as well as optimizing diagnostic and therapeutic strategies to minimize the likelihood of misdiagnosis.

Ethical Statement and Informed Consent

This study and the publication of case details were approved by the Ethics Committee of Binzhou Medical University Hospital. Written informed consent was obtained from the patient for publication of this case report and accompanying images, in accordance with institutional publication ethics guidelines.

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Disclosure

The authors declare that they have no competing interests in this work.

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