Hidden Within: Pulmonary Nocardiosis in an Immunocompetent COPD Patient

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This report presents the case of an 86-year-old man with chronic obstructive pulmonary disease (COPD) managed since 2018 with inhaled corticosteroids, long-acting muscarinic antagonists, long-acting beta-agonists, and roflumilast. He was admitted to the medical intensive-care unit with acute respiratory failure due to severe pneumonia. Imaging revealed left lower lobe consolidation. Despite treatment with piperacillin/tazobactam and methylprednisolone, his condition worsened, necessitating bronchoscopy. Sputum samples identified *Nocardia* species, confirming pulmonary nocardiosis, and he was started on trimethoprim-sulfamethoxazole (TMP-SMX) therapy. The case highlights the risks associated with long-term corticosteroid use in COPD patients, which may predispose them to opportunistic infections such as nocardiosis. The patient's severe COPD and potential macrophage dysfunction likely contributed to the development of nocardiosis This case underscores the importance of the early recognition and appropriate treatment of pulmonary nocardiosis to reduce associated morbidity. Bronchoscopy is crucial for diagnosing difficult-to-culture organisms in patients unresponsive to standard treatment, and gene sequencing offers promise for rapid, accurate detection. The patient showed clinical improvement with TMP-SMX therapy, with follow-up imaging indicating partial resolution. Continued outpatient care is scheduled, emphasizing vigilance in managing high-risk COPD patients, particularly in tropical regions such as Puerto Rico.

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In the realm of infectious diseases, nocardiosis stands out as a rare opportunistic bacterial infection, typically observed in immunocompromised patients. The bacterium is acquired by inhaling fragmented mycelia found in the soil. According to the Centers for Disease Control and Prevention (CDC), the United States witnesses 500 to 1,000 new cases, annually, emphasizing its rarity (1). *Nocardia*, a member of the class Actinomycetales, straddles the line between bacteria and fungi, displaying aerobic, Gram-positive characteristics and a penchant for branching filamentous growth (2). With a history of scientific discovery dating back to its first isolation by Edmond Nocard in 1888, the genus *Nocardia* has shaped a taxonomic landscape encompassing 119 species, of which 54 can clinically affect human hosts (3). Notably, *Nocardia* asteroides is a globally dominant species, and *Nocardia* brasiliensis is prevalent in tropical and subtropical climates (2,4). Our research did not yield specific epidemiological data for Puerto Rico or for similar cases involving patients with chronic obstructive pulmonary disease (COPD) alone.

While historically linked to immunocompromised states, recent insights have broadened our understanding, revealing the potential for infection in immunocompetent patients.

Case Report

We present the case of an 86-year-old male with a history of COPD—on inhaled corticosteroids/long-acting muscarinic antagonist/long-acting beta-agonist (ICS/LAMA/LABA) and roflumilast on an outpatient basis since 2018—who was admitted to the medical intensive-care unit due to acute respiratory failure caused by severe pneumonia. Imaging revealed left lower lobe consolidation with air bronchograms (Figure 1). A record review revealed multiple hospitalizations for COPD exacerbation, with similar findings noted during an admission nine months earlier. Despite being treated with intravenous (IV) piperacillin/tazobactam and IV methylprednisolone, the patient deteriorated exhibiting thick, non-malodorous secretions for which a bronchoscopy was performed.

Endobronchial specimens tested negative for acid-fast bacilli, KOH preparation, and cultures. Sputum samples were examined under a microscope, and special acid-fast staining revealed short, filamentous, bead-like bacteria consistent with the morphology of *Nocardia* species (Figure 2). A diagnosis of pulmonary nocardiosis was made, and the patient was started on trimethoprim-sulfamethoxazole (TMP-SMX) therapy. A brain CT scan was negative for any acute intracranial process.

Discussion

Nocardia isolates have traditionally been susceptible to TMP-SMX, but there has been an increase in the number of resistant isolates. Therefore, it is advisable to consider treatment regimens including TMP-SMX, imipenem, and amikacin when this kind

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Figure 1. High-resolution computed tomography (HRCT) of the chest showing parenchymal changes on the day of admission (left) and improvement of parenchymal changes after three months of treatment (right).

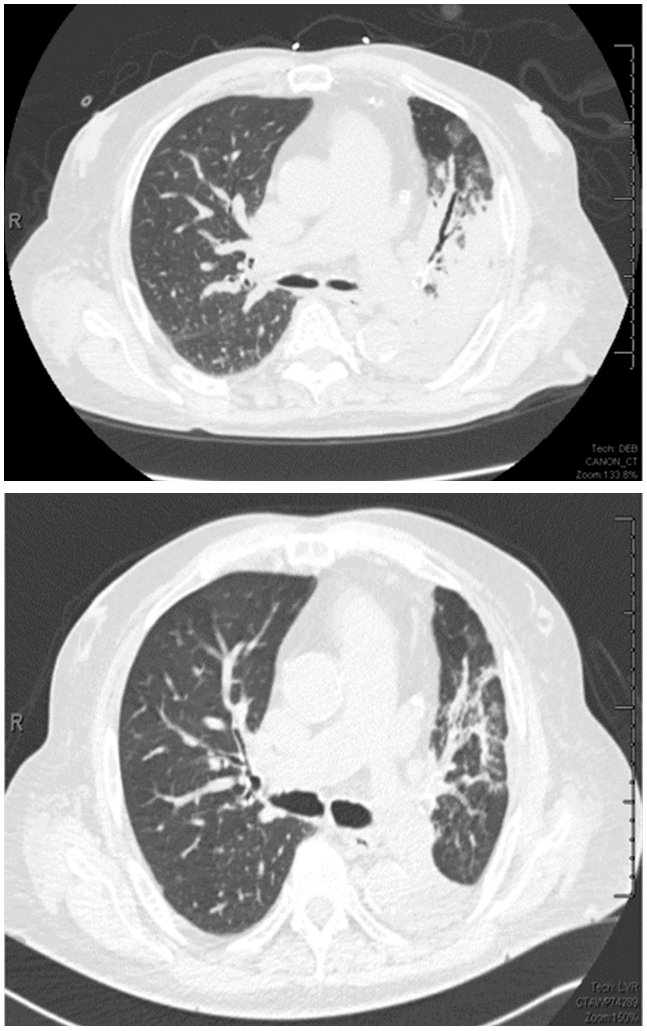
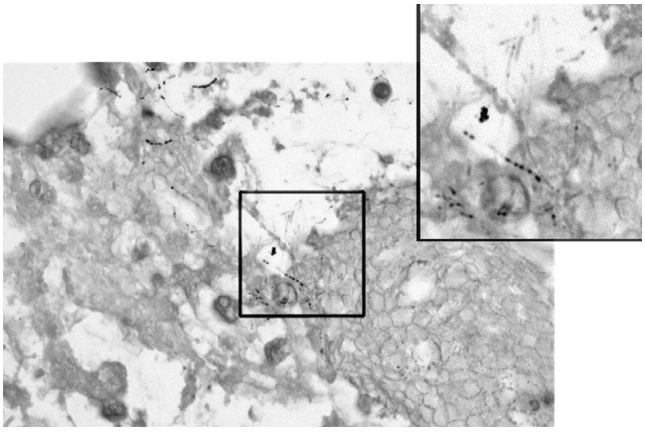


Figure 2. Histology using special acid-fast staining, showing an enhanced zoom of the area of interest. Short, filamentous, bead-like bacteria consistent with the morphology of *Nocardia* species are noted.



of resistance is suspected or confirmed. In our case, we could not culture the specific *Nocardia* sp. to determine its susceptibility; the patient's clinical improvement in therapy suggests that the treatment was effective.

The administration of high-dose, short-term corticosteroids is a common therapeutic approach for managing COPD exacerbations. Yet, the potential impact of long-term corticosteroid use on infection risk remains uncertain. Notably, immunosuppressive agents, such as the corticosteroids used in chronic corticosteroid therapy, have been strongly associated with an elevated risk of nocardiosis in solid-organ transplant recipients (5,6). This susceptibility is believed to stem from the inhibitory effect of steroids on T-cell function (7). Our patient had been on an ICS/LAMA/LABA inhaler regimen since 2018 and had previously received short courses of oral prednisone for COPD exacerbations, with the last use documented six months before this most recent admission. In addition, our patient's absolute neutrophil count was adequate before and during admission, suggesting that our patient was unlikely to have been immunocompromised during the initial infectious course of his disease.

We suspect that the severe nature of the patient's underlying COPD predisposed him to opportunistic infections such as nocardiosis. Research has shown that individuals with COPD exhibit increased incidence of macrophage dysfunction, adding to the complexity of *Nocardia's* pathogenicity (8). Through mechanisms such as cord factors and trehalose dimycolate, *Nocardia* diminishes the integration of phagosomes and lysosomes, thus evading phagocytosis by macrophages (9). Furthermore, evidence indicates a correlation between the airway microbiome and the inflammatory phenotype observed in COPD, offering valuable insights into the underlying pathophysiology of the disease.

Studies have demonstrated the proliferation of specific bacterial species within the COPD patient population, including Pseudomonas, Haemophilus, Klebsiella, and Actinomyces, the latter belonging to the taxonomical class of *Nocardia*. These bacteria exhibit elevated TNF-α and Th1 inflammatory signatures, contributing to COPD exacerbations and structural bronchial damage (10). Again, their colonization of the bronchus disrupts ciliary motility, worsening epithelial damage and causing chronic structural alterations in bronchial architecture, thereby perpetuating bacterial colonization (6).

Conclusion

Though rare, pulmonary nocardiosis has mortality rates ranging from 7% to nearly 39% (5,7), particularly in COPD patients. This case highlights COPD as a risk factor for pulmonary nocardiosis and emphasizes the need for early diagnosis to reduce morbidity. Recognizing uncommon infections, especially in tropical regions such as Puerto Rico, is vital, as tropical regions may have higher environmental exposure to opportunistic pathogens. Bronchoscopy remains crucial for diagnosing infections unresponsive to standard antibiotics, as conventional cultures often have low sensitivity. Emerging techniques such as 16S rRNA

sequencing could improve the rapid identification of *Nocardia*, enabling timely and targeted treatment (11).

Our patient continues TMP-SMX therapy (4), with follow-up imaging showing partial resolution of lung consolidation (Figure 1). Outpatient care is ongoing.

Resumen

Este informe presenta el caso de un hombre de 86 años con enfermedad pulmonar obstructiva crónica (EPOC) tratada con corticosteroides inhalados, antagonistas muscarínicos de acción prolongada, agonistas beta de acción prolongada y roflumilast desde 2018. Fue ingresado con insuficiencia respiratoria aguda debido a neumonía grave. La imagen reveló consolidación en el lóbulo inferior izquierdo. A pesar del tratamiento con piperacilina/tazobactam y metilprednisolona, su condición empeoró, lo que requirió una broncoscopía. Las muestras de esputo identificaron especies de *Nocardia*, confirmando nocardiosis pulmonar, y se inició terapia con trimetoprima-sulfametoxazol (TMP-SMX). La discusión destaca los riesgos asociados con el uso prolongado de corticosteroides en pacientes con EPOC, lo cual puede predisponerlos a infecciones oportunistas como la nocardiosis. La grave EPOC del paciente y una posible disfunción de los macrófagos probablemente contribuyeron a esta infección. Este caso subraya la importancia de la detección temprana y el tratamiento adecuado de la nocardiosis pulmonar para reducir la morbilidad. La broncoscopía es fundamental para el diagnóstico de organismos difíciles de cultivar en pacientes que no responden al tratamiento, y la secuenciación genética ofrece una prometedora detección rápida y precisa. El paciente mostró mejoría clínica con TMP/SMX, y las imágenes de seguimiento indicaron una resolución parcial. Se programó atención ambulatoria continua, enfatizando la vigilancia en el manejo de pacientes con EPOC de alto riesgo, particularmente en regiones tropicales como Puerto Rico.

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