

**Case Study**

**CASE SERIES OF ISOLATED PULMONARY NOCARDIOSIS AMONG POST-COVID-19 INDIVIDUALS**

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**ABSTRACT**

Nocardia infections are rare in an immunocompetent and healthy individual. It is frequently diagnosed and reported very late during the disease. Here we present an interesting case series of isolated pulmonary nocardiosis among post COVID-19 patients. A 45-year-old male presented to general medicine OPD with breathlessness and cough with expectoration. The patient was a known case of diabetes. A sputum sample was sent for culture, gram, and acid-fast stain, and the nasopharyngeal swab was sent for RT-PCR and turned out to be COVID-19 negative. Gram stain showed numerous pus cells with filamentous hyphae-like structures. Nocardiosis was strongly considered based on imaging morphology. A 65-year-old female presented to OPD with fever, respiratory distress, and expectorating cough for one month. The patient was a not known case of diabetes and hypertension. The patient was diagnosed with pneumonia and had a history of COVID-19. The microscopic examination of the sputum sample revealed no fungal elements. The Gram and Ziehl-Neelsen stain showed pus cells with filamentous bacilli and no acid-fast bacilli. A 50-year-old male presented to general medicine OPD with breathlessness and expectorating cough for four weeks. The patient was a not known case of diabetes and hypertension. The sputum sample was negative for ZN stain; the Gram stain showed numerous pus cells with filamentous hyphae-like structures. The modified acid-fast staining was done for sputum and BAL samples in all cases showed filamentous weak acid-fast bacilli resembling Nocardia species. The patient did well with cotrimoxazole and was discharged later. The differential diagnosis of nocardia should always be in mind in case of lung infections. All respiratory samples must also be screened for Nocardia. The early diagnosis and management of pulmonary nocardiosis decide the patient's prognosis.

**Keywords:** Pulmonary nocardiosis, Post-covid-19, *Nocardia asteroides*, Trimethoprim-sulfamethoxazole

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**INTRODUCTION**

Nocardia falls under the suborder *Corynebacterineae* along with Mycobacterium and Corynebacterium. They are ubiquitous, aerobic, gram-positive bacilli with high G: C content in their DNA [1-3]. The quantity of mycolic acid in Nocardia's cell wall makes it differ from other genera. In 1889, a French veterinarian Edmond Nocard discovered the genus Nocardia. Based on the new molecular techniques and drug resistance to sulfonamides after its treatment, Nocardia has been recognized as a human pathogen with many species [1, 4-6]. Nocardia infections are rare in immunocompetent and healthy individuals. The human infections are localised or disseminated among immunosuppressed persons [4]. No cases have been reported among immunocompetent individuals, even with co-morbidities [7]. The most affected organ is the lungs because the mode of transmission is airborne. Among the total cases of nocardiosis, about 70% are pulmonary nocardiosis [8]. It is frequently diagnosed and reported very late during disease, and the incidence of nocardiosis is also very limited [9]. We present case series of isolated pulmonary nocardiosis among post-COVID-19 patients.

**Case descriptions**

**Case 1**

A 45 y old male presented to general medicine OPD with breathlessness and cough with expectoration for three weeks. The patient was a known case of diabetes and was on anti-diabetic drugs. On clinical examination of the respiratory system, there was wheeze and crackles; other system examinations were within normal limits. The patient was diagnosed with acute bronchitis with secondary

pneumonia. He was admitted, the sputum sample was sent for culture, gram, and acid-fast stain, and other routine investigations. The nasopharyngeal swab was sent for RT-PCR, and it was COVID-19 negative. All blood investigations were within normal range except blood glucose. The patient was given insulin and empirical antibiotics. The sputum sample was negative for ZN stain; Gram stain showed numerous pus cells with filamentous hyphae-like structures (fig. 1). Hence Gomori's methanamine silver stain was done and showed no fungal elements. Initially, the patient was managed with a piperacillin and tazobactam combination and completed monitoring.

The microscopic examination of the sputum sample after treatment with 40% KOH and special stains revealed no fungal elements. The sputum was cultured in blood, chocolate, MacConkey and Sabouraud dextrose agar. The chest X-ray showed bilateral consolidation in the right lower lobe with veiling air space opacities (fig. 2). The chest CT showed bilateral scattered ground glass opacities and multifocal inhomogeneous consolidation with small cavitary lesions in the middle lobe. It was consistent with pneumonia, extensive subcutaneous emphysema and minimal pneumomediastinum. (fig. 3). Patient was not at risk for contact with Tuberculosis or fungal infection; hence lymph proliferative disorders or Nocardiosis was strongly considered based on imaging morphology. The modified acid-fast staining for sputum and BAL samples showed filamentous weak acid-fast bacilli resembling Nocardia species (fig. 4). The patient did well with Trimethoprim and sulfamethoxazole combination with linezolid and spO2 monitoring, and discharged later. Further follow-up ensured about completion of three months of antibiotics and improvement based on clinical findings and radiologically.

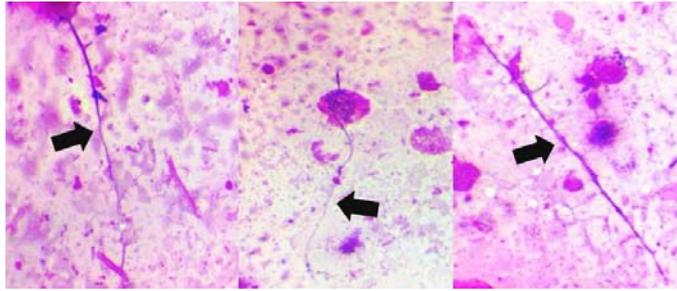


Fig. 1: Gram stain showing numerous pus cells with gram-positive filamentous hyphae-like structures

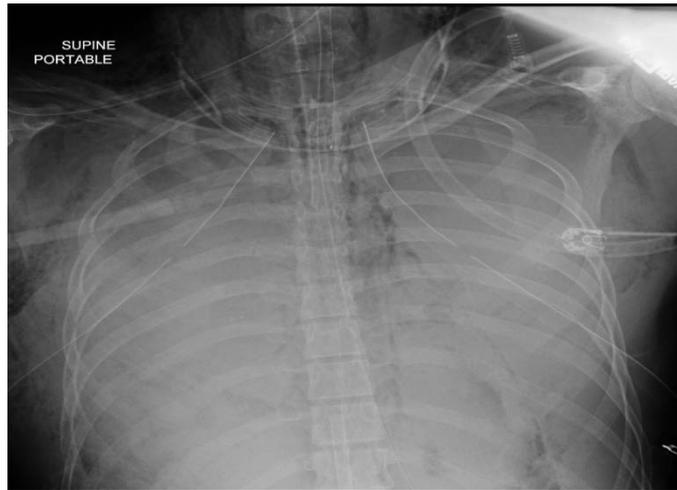


Fig. 2: Chest radiography showed consolidation in the right lower and middle lobe with complete opacification and bilateral hemithorax; apically oriented bilateral chest tubes with end tracheal tube and NG tube in an appropriate position. (Multifocal pneumonia with ARDS)

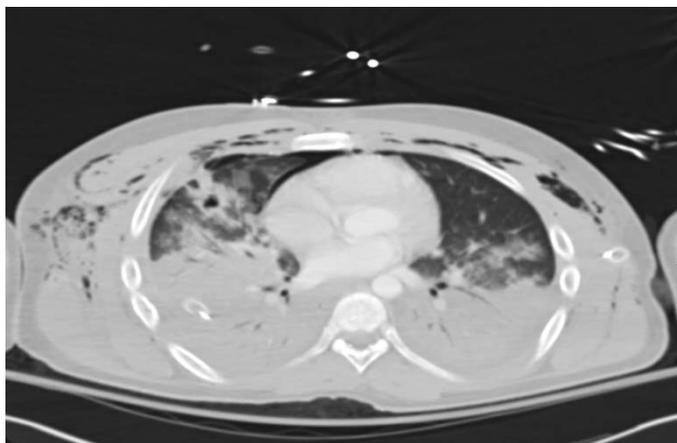


Fig. 3: The chest CT showed scattered ground glass opacities bilaterally and multifocal inhomogeneous consolidation with small cavitory lesions in the middle lobe (pneumonia, extensive subcutaneous emphysema and minimal pneumomediastinum)

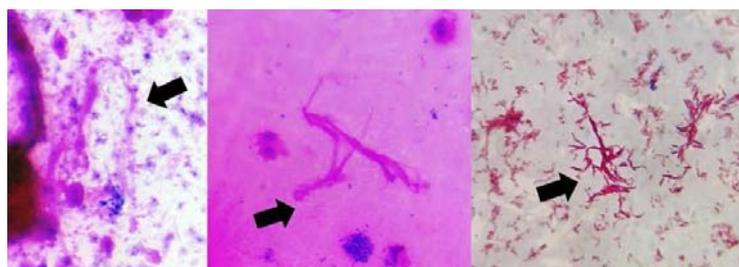


Fig. 4: The modified acid fast staining-showing weak filamentous acid-fast bacilli resembling nocardia species

## Case 2

A 65-year-old female presented to OPD with fever, respiratory distress, pleuritic chest pain, expectorating cough, generalized body pain, weight loss and loss of appetite for one month. The patient was a not known case of diabetes and hypertension. The patient was diagnosed with pneumonia and had a history of COVID-19. He was admitted, and RT-PCR (COVID-19), sputum sample for culture, gram stain, acid-fast stain and other routine investigations was done. All blood investigations showed anemia, neutrophilia and hyponatremia; the patient was started with piperacillin and tazobactam.

The microscopic examination of the sputum sample after treatment with 40% KOH and special fungal stains revealed no fungal elements. The Gram and Ziehl-Neelsen stain showed pus cells with filamentous bacilli (fig. 1) and no acid-fast bacilli, respectively. The Chest X-ray showed nonhomogenous opacities in the lower lobe. The lung CT showed heterogeneous opacities and no evidence of COVID-19. The modified acid-fast staining for sputum and BAL samples showed filamentous weak acid-fast bacilli resembling *Nocardia* species (fig. 4). After 24 h, the RT-PCR for SARS-COV2 virus was negative. The patient did well with trimethoprim-sulfamethoxazole in combination with linezolid and spO2 monitoring.

## Case 3

A 50-year-old male presented to general medicine OPD with breathlessness and expectorating cough for four weeks. The patient was a not known case of diabetes and hypertension. On clinical examination of the respiratory system, there was wheeze and crackles; other system examinations were within normal limits. The patient was admitted, the sputum sample was sent for culture, Gram, and acid-fast stain and other routine investigations. The nasopharyngeal swab was sent for RT-PCR, and it was COVID-19 negative. All blood investigations were within normal range except for neutrophilia and hyponatremia. The sputum sample was negative for ZN stain, the Gram stain showed numerous pus cells with filamentous hyphae-like structures (fig. 1), and the Gomori's methanamine silver stain showed no fungal elements. With our experience of managing 2 nocardial infections, we started empirical cotrimoxazole and meropenem sulbactam combination. The chest X-ray showed consolidation in the right lower lobe with bilateral veiling air space opacities. The Chest CT was recommended and similar findings were noted as before.

The microscopic examination of the sputum sample after treatment with 40% KOH and special stains revealed no fungal elements. The modified acid-fast staining for sputum and BAL samples showed filamentous weak acid fast bacilli resembling *Nocardia* species (fig. 4). The patient did well with cotrimoxazole and spO2 monitoring; his vital parameters were stable and discharged later. After four weeks repeat sample was sent for sputum culture, and CT-chest was also done. The RT PCR result was negative, CT-chest was normal, the sputum culture showed no growth, and the patient was stable.

## DISCUSSION

*Nocardia* species are gram-positive, non-spore forming filamentous (mycelia-like) and acid-fast bacilli [10]. They are ubiquitous and saprophytic found in soil and water. The different modes of infections are inhalation, invasion through cuts and abraded skin [10, 11]. Disease by nocardia was previously thought to be uncommon, but since 1976, many cases have been reported in western and tropical countries, as per CDC surveys. In recent years, the incidence of nocardial infections has been increasing among immunocompromised individuals with HIV, organ transplantation, prolonged corticosteroids and anti-cancer therapy and unlikely predisposes in COPD patients too [12-16].

The dissemination of nocardia can be seen most commonly in the lungs, up to 77 %, followed by others like CNS, skin and rarely CVS, ocular and bones. The most common mode of dissemination is hematogenous and lymphatic route, which accounts for 25% to 50% of cases. 30 to 80% of the mortality rate was recorded in localized pleura pulmonary involvement among immunocompromised patients [15, 16]. The nocardial disease development in most studies is 4 to 24 w post-transplant procedures. During this period,

continuous treatment with steroids is attributed to immunosuppression [17]. The steroids-induced immunosuppression will produce an inhibitory effect on monocytes, lymphocytes and granulocytes, leading to rare bacterial infections [18].

Like other bacterial and fungal infections, pulmonary nocardiosis presents with usually non-specific symptoms and sub-acute and chronic duration. The common symptoms are fever, cough, body pain and pleurisy. In tuberculosis (TB) endemic countries, presenting symptoms mimics TB, and anti-TB therapy will be started. *Nocardia* must permanently be excluded in cases with similar clinical presentation and not responding to anti-TB treatment [18]. The radiological features remain non-specific with unilobar or multi-lobar consolidation, nodular or reticulonodular infiltrations and solitary lung masses. Up to 30% of cases can present with cavitations, most commonly in the apical region [19, 20]. The drug of choice in the management of nocardiosis is still cotrimoxazole. Amikacin, imipenem, ceftriaxone, minocycline, levofloxacin, linezolid, and amoxicillin-clavulanic acid are alternative medicines for treatment [20-22].

## CONCLUSION

The differential diagnosis of nocardia should always be in our mind in case of lung infections, especially pneumonia with atypical radiological presentations and empirical treatment failure. All respiratory samples like sputum, pleural fluids and BAL must also be screened for suspected *Nocardia* cases. The early diagnosis and management of pulmonary nocardiosis with specific antimicrobial therapy decides the patient's prognosis. In our third case we considered nocardiosis as differential diagnosis and managed keenly with a combination of cotrimoxazole, meropenem, and sulbactam, saved the patient at the earliest. The recent increase in cancers, transplantation techniques, use of steroids in COVID-19 and other conditions should increase the suspicion of pulmonary nocardiosis.

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## AUTHORS CONTRIBUTIONS

The lab diagnosis, complete write-up, photos and editing were done by (Prasanna S, First and Corresponding author). The lab diagnosis and reporting were done by (Mayuri Mahajan, Second author). Editing and compilation were done by (Nikhil Kumar Das, third author). The supportive clinical diagnosis was done by (Nikhil Mahajan, the fourth author). The editing of photos were done by (Chandana S, Fifth author)

## CONFLICT OF INTERESTS

Declared none

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