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Nocardiosis –A Series of Four Case Reports

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Authors' contributions

This work was carried out in collaboration between all authors. Author SS and LV designed the study performed. Author SS wrote the protocol, and wrote the first draft of the manuscript. Authors SS, PK, and LV managed the analyses of the study. Authors SS, PK and LV managed the literature searches. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Aim: *Nocardia* spp are ubiquitous soil organisms that often infect patients with underlying compromised immunity, pulmonary disease or history of surgery or trauma. The diagnosis of nocardiosis can be missed because there are no characteristic symptoms. Pulmonary nocardiosis is a major cause of morbidity and mortality in immunocompromised patients

Presentation of Case: We present 3 cases of pulmonary nocardiosis and one case of disseminated nocardiosis, that were culture proven

Conclusion: With increase in immunocompromised patients, early recognition and initiation of appropriate treatment can lead to successful outcome.

Keywords: Nocardia; pulmonary; disseminated; MALDI-TOF; immunocompromised.

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1. INTRODUCTION

Nocardia species are ubiquitous soil organisms that often infect patients with underlying immune compromise, pulmonary disease, or a history of surgery or trauma [1]. The main route of acquisition is through direct inhalation of contaminated particles or by direct inoculation through the intact skin. The diagnosis of nocardiosis can easily be missed because there are no characteristic symptoms. The manifestations of nocardiosis can be solely pulmonary, but *Nocardia* spp can also disseminate from a pulmonary or cutaneous focus to virtually any organ [2]. Pulmonary nocardiosis is a major cause of morbidity and mortality in immunocompromised patients. We hereby report 3 cases of pulmonary nocardiosis and one case of disseminated nocardiosis, probably caused by rare species of *Nocardia.*

2. CASE REPORT

2.1 Case 1

A 40-year-old male, known case of post renal transplant on immunosuppression was admitted with complaints of fever, shortness of breath, fatiguability and vomiting for 2 weeks. High-resolution computed tomography (HRCT) chest revealed right upper lobe fibrocavitary lesion, left lower lobe consolidation, left pleural effusion and nodular lesion on left upper lobe. Ultrasonogarm (USG) abdomen revealed contracted naïve kidney, minimal ascites with perisplenic fluid, bilateral pleural effusion and pericardial effusion. Bronchoalveolarlavage (BAL) was done and the sample was sent to microbiology. *Nocardia* spp was isolated from the BAL. It was identified as as *Nocardia cyriacigeorgica,* by the Matrix assisted laser desorption ionization-time of flight mass spectrometry (MALDI TOF) (Bruker Daltonic MALDI Biotyper).*Klebsiella pneumonia* also grown in culture which was sensitive to only to colistin. Patient was initiated on intravenous meropenem 1 g twice daily, colistin 1 MU twice daily, amikacin 1 g twice daily, oral septran double strength twice daily. He had persistent hyponatremia, falling hemoglobin decreased platelet count in hospital course. In view of deranged prothrombin time, fresh frozen plasma was given. In spite of best efforts his condition deteriorated. He was intubated and supported with ventilation. Inspite of best efforts patient condition could not be revived and had sudden cardiac death.

2.2 Case 2

A 60- year old female, non-diabetic, hypertensive was admitted in our hospital in an intubated state with tracheostomy on mechanical ventilation. She was diagnosed to have disseminated nocardiosis (cerebral, pulmonary, and cutaneous) with sepsis, shock and respiratory failure at an outside hospital. She was received at our hospital in a vegetative state with poor Glasgow Coma Scale and on ionotropes.

On examination patient was in altered sensorium, anasarca and obeying commands. Cutaneous wheel lesions were seen on the body with purulent discharge. Multiple erythematous patches were seen over both upper and lower limb and some were healed with hyper pigmented lesion. Pulse rate was feeble, blood pressure was 90/60 mmHg on ionotropes.

Central nervous system examination revealed areflexic quadriparesis. Magnetic resonance imaging (MRI) brain revealed mild cerebral atrophy with multiple small lytic lesions, many with peripheral enhancement in bilateral cerebellum, cerebral hemispheres, brain stem without obvious edema and few eccentric nodules .computed tomography (CT) brain revealed multiple small ill-defined hypoechoic lesions in cerebral cortex, white matter, cerebral hemispheres and multiple lytic lesions in calvarium. CT plain thorax revealed paramediastinal lung mass in left lower lobe, multiple bilateral lung nodules with cavitary lesions in right lower lobe and enlarged right hilar lymph node.

The *Nocardia* isolates from Blood culture and pus culture from skin lesions were identified as *Nocardia otitidiscaviarum* by MALDI TOF. Blood culture also showed growth of *Acinetobacter baumanii*. As *Nocardia otitidiscaviarum* is commonly resistant to trimethoprim-sulfamethoxazole, patient was treated with intravenous ceftriaxone 2 g twice daily, intravenous amikacin 1 g once daily and intravenous colistin 1MU twice daily and other supportive measures.

Patient sensorium was not improved. Neurologist opinion was taken who advised to continue same treatment. Patient developed fever spikes and hypotension and was treated accordingly with ionotropes. Due to financial constraints patient attendants requested for discharge and left against medical advice.

2.3 Case 3

A 20 year old female, live post renal transplant on triple immunosuppression, came with complaints of loose motions which decreased with probiotics, vomiting for 1 week associated with food and decreased appetite, fever with chills and rigor, productive cough, abdominal discomfort. On examination, patient was malnourished and dehydrated. HRCT revealed mild ground glass appearance. CT chest revealed soft tissue density left nodular opacities with surrounding echo. She was started with intravenous meropenem 500 mg twice daily. Bronchoscopy was done and bronchial wash was sent to microbiology which grew *Nocardia farcinica* (identified by MALDI TOF).Patient was started on oral septran double strength. Her general condition improved and was discharged with advice on regular follow up.

2.4 Case 4

A 52 year old male ,animal vendor, known HIV 1 positive, on antiretroviral therapy came with complaints of swelling in the left side of chest with fever on and off for 3 months. On examination, he was ill built with multiple soft, non tender chest wall swellings. Chest X ray was suggestive of left empyema and loculated effusion.

CT chest was suggestive of large loculated pleural based collection in left pleural space showing extra thoracic and abdominal wall extension. Non-contrast computerized tomography (NCCT) chest was suggestive of loculated left pleural effusion with osteomyelitic changes in left 10^{th} and 11^{th} rib with chest wall collection. Empirically he was started on intravenous ceftriaxone 1 g twice daily and intravenous clindamycin 600 mg thrice daily. Loculated pleural effusion was drained through pigtail and the chest wall abscess drained. Cytology was suggestive of inflammatory cells. Culture isolate was identified as *Nocardia asiatica* by MALDI TOF. He was started on intravenous cotrimoxazole 5-10 mg/kg. Patient's condition deteriorated and inspite of best efforts patient could not be revived.

2.5 Microbiology

Bronchial wash from 3 patients with pneumonia and purulent aspirate from skin lesions (Fig. 1) from the patient with disseminated Nocardiosis were processed as per recommended guidelines by Gram stain and culture on 5% sheep blood agar and chromogenic agar and incubated aerobically at 37°C. Blood cultures, received from the patient with disseminated Nocardiosis, were processed using the BacT/Alert system (*BioMérieux Marcy l'Etoile, France)*. Direct Gram stain of specimen and the positive blood culture showed Gram positive branching filaments suggestive of *Nocardia* spp (Fig. 2a). 1% Acid fast stain showed partially acid fast thin branching filaments. (Fig.2b).The colony morphology of the isolates is shown in Fig. 3. Further species identification was attempted on the Bruker Daltonic MALDI Biotyper at Microbiological laboratory, Coimbatore, India.

3. DISCUSSION

Nocardiosis is caused by Gram-positive, weakly acid-fast, filamentous aerobic actinomycetes in the genus. The disease is caused primarily by *N.asteroides, N. farcinica, N. nova, N. brasiliensis* and *N. otitidiscaviarum* in general population and can also cause opportunistic infection in immunocompromised patients [3]. Pulmonary and systemic infections are common in immunocompromised patients with depressed cell-mediated immunity [4].

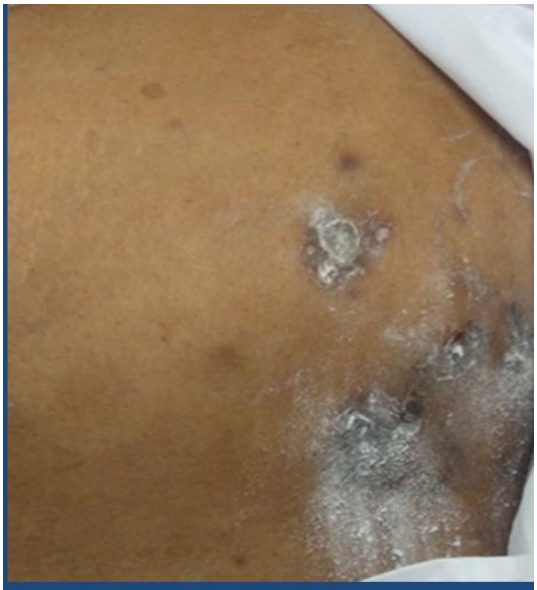

Fig.1. Cutaneous wheel lesions in disseminated Nocardiosis

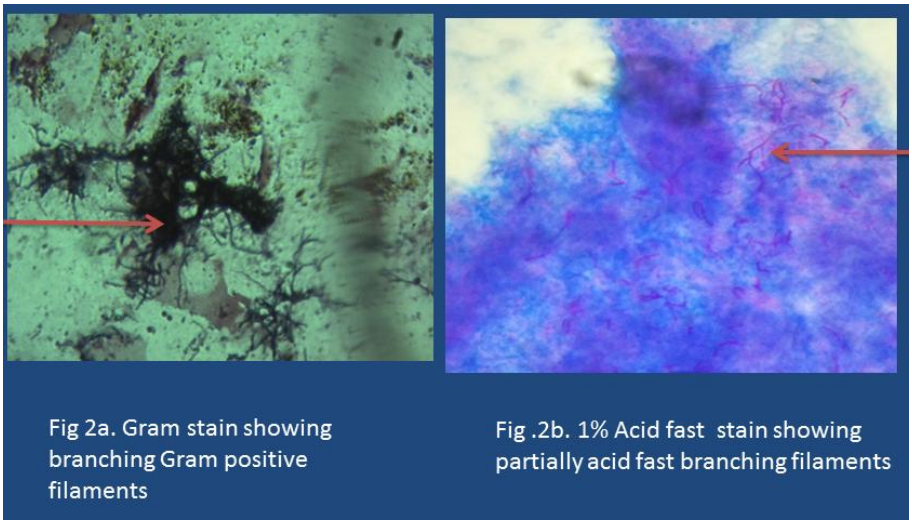

Fig 2a. Gram stain showing branching Gram positive filaments

Fig .2b. 1% Acid fast stain showing partially acid fast branching filaments

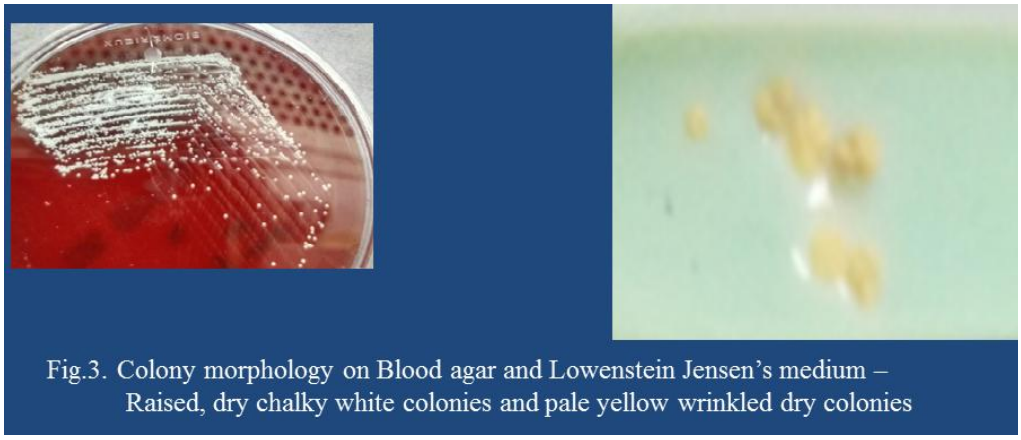

Fig.3. Colony morphology on Blood agar and Lowenstein Jensen's medium – Raised, dry chalky white colonies and pale yellow wrinkled dry colonies

Phagocytic and cell mediated immunity have important role in protecting against disseminated disease [5]. We isolated *N. farcinica, N. asiatica, N. cyriacigeorgica* and *N. otitidiscaviarum* from four cases, three of them are immunocompromised which is a major risk factor for Nocardiosis and one had disseminated nocardiosis with an unknown underlying condition.

The most common predisposing factor was organ transplantation followed by malignancies like leukemia and lymphoma and Acquired Immunodeficiency Syndrome [6]. Two of our cases were post renal transplant and one patient was a known HIV positive patient.

Three of our patients had pulmonary nocardiosis while one had disseminated nocardiosis involving skin, brain, lungs and blood. Cutaneous nocardiosis occurs via inoculation while pulmonary nocardiosis occurs through inhalation.

As *Nocardia* spp differ in their responses to antimicrobials accurate identification of species are becoming important, for studies of antimicrobial susceptibility, clinical and epidemiological investigations [3].

Identification by conventional phenotypical methods is a fastidious and time-consuming process, often requiring days to complete identification, owing to the slow growth and limited reactivity of these bacteria. Species identification was attempted using the MALDI-TOF, a rapid diagnostic tool, which analyzes the protein composition of a bacterial cell and help in identification of species [7]. However, additional spectral databases have to be included for identification of *Nocardia* on the MALDI TOF, the species confirmation warrants16S rRNA genetic sequencing.

The signs and symptoms of *Nocardia* mimic conditions like tuberculosis, fungal pneumonia or

lung cancer, hence it should be always considered as a differential diagnosis in immunocompromised patients when they do not respond to standard treatment [8].

Treatment of Nocardiosis varies depending on the species involved, condition of the patient and also the site of involvement. Duration of treatment is generally prolonged to minimize risk of disease relapse. Treatment should be given for 6-12 months for immunocompetent patients with non-CNS nocardiosis and 12 months or longer for immunosuppressed patients with CNS disease. For patients on immunosuppressive treatment, maintenance therapy may be prolonged and they should be monitored clinically [9].

Trimethoprim-sulfonamides, aminoglycosides, linezolid, amoxicillin-clavulanate, imipenem, cefotaxime, ceftriaxone are considered drugs of choice for nocardiosis therapy in animals and people. Combined therapy using amikacin with sulfonamides, and amikacin with imipenem or cephalosporins is recommended.

The standard treatment of nocardiosis is usually a sulfa-containing regimen, but there is increasing resistance to the drug due to its adverse reactions, and the potential for nephrotoxicity in transplant recipients on cyclosporine. Resistance to sulphonamides is on the rise especially among *N.farcinica* and *N. otitidiscaviarum* isolates.

Three of our patients were treated with oral and intravenous septran while one patient was treated with intravenous ceftriaxone and amikacin.

Depending on the site and the extent of infection combined with underlying host factors, nocardiosis has a variable prognosis, cure rates with appropriate therapy are approximately 100% in skin and soft-tissue infections, 90% in pleuro-pulmonary infections, 63% in disseminated nocardiosis and 50% in patients with brain abscesses. Three patients succumbed to infection while one patient survived with an advice to follow up [9].

4. CONCLUSION

As *Nocardia* spp differ in their responses to antimicrobials, accurate identification of species are becoming important, for studies of antimicrobial susceptibility, clinical and epidemiological investigations which can be done by newer diagnostic tools like MALDI-TOF, with amplified database to improve the results. With increase in immunocompromised patients, early recognition and initiation of appropriate treatment can lead to successful outcome.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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