

1 Case study

2 **Nocardiosis –A series of four case reports**

3 **Abstract**

4 **Aim**

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

10 **Presentation of case**

11 We present 3 cases of pulmonary nocardiosis and one case of disseminated
12 nocardiosis, that were culture proven

13 **Conclusion**

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

16 **Keywords**

17 *Nocardia*;pulmonary;disseminated;MALDI-TOF;immunocompromised.

18 **Introduction**

19 *Nocardia* species are ubiquitous soil organisms that often infect patients with
20 underlying immune compromise, pulmonary disease, or a history of surgery or
21 trauma[1].The main route of acquisition is through direct inhalation of
22 contaminated particles or by direct inoculation through the intact skin. The
23 diagnosis of nocardiosis can easily be missed because there are no characteristic
24 symptoms. The manifestations of nocardiosis can be solelypulmonary, but
25 *Nocardiaspp* can also disseminate from a pulmonary or cutaneous focus to
26 virtually any organ[2] Pulmonarynocardiosis is a major cause of morbidity and
27 mortality in immunocompromised patients. We hereby report3 cases of pulmonary
28 nocardiosis and one case of disseminated nocardiosis, probably caused by rare
29 species of *Nocardia*.

30 **Case report**

31 **Case 1**

32 A 40-year-old male, known case of post renal transplant on
33 immunosuppression,was admitted with complaints of fever,shortness of
34 breath,fatiguability and vomiting for 2 weeks.High-resolution computed
35 tomography(HRCT) chest revealed right upper lobe fibrocavitary lesion, left lower
36 lobe consolidation, left pleural effusion and nodular lesion on left upper lobe.

Ultrasonogram(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. *Nocardiaspp* was isolated from the BAL. It was identified as *Nocardiacyriacigeorgica*,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 tocolistin.Patientwas initiated on intravenous meropenem 1g twice daily, colistin 1 MU twice daily,amikacin 1g 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.

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,cutaneous)with sepsis, shock and respiratory failureat an outside hospital.She was received at our hospital in a vegetative statewith poor Glasgow Coma Scale and on ionotropes.

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

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

71 The Nocardia isolates from Blood culture and pus culture from skin lesions were
72 identified as Nocardiaotitidiscaviarumby MALDI TOF.Blood culture also showed
73 growth of Acinetobacter baumannii.As Nocardiaotitidiscaviarum is commonly
74 resistant to trimethoprim-sulfamethoxazole, patient was treated with intravenous
75 ceftriaxone 2g twice daily, intravenous amikacin 1 g once daily and intravenous
76 colistin 1MU twice daily and other supportive measures

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

81 **Case 3**

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

93 **Case 4**

94 A 52 year old male , animal vendor, known HIV 1 positive, on antiretroviral
95 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 extrathoracic and abdominal wall extension. Non-contrast computerized tomography (NCCT) chest was suggestive of loculated left pleural effusion with osteomyelitic changes in left 10th and 11th rib with chest wall collection. Empirically he was started on intravenous ceftriaxone 1g 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 5-10mg/kg. Patient's condition deteriorated and in spite of best efforts patient could not be revived.

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.

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 infection are common in immunocompromised patients with depressed cell-mediated immunity[4].

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

133 Nocardiosis and one had disseminated nocardiosis with an unknown underlying
134 condition.

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

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

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

145 Identification by conventional phenotypical methods is a fastidious and time-
146 consuming process ,often requiring days to complete identification, owing to the
147 slow growth and limited reactivity of these bacteria. Species identification was
148 attempted using the MALDI-TOF, a rapid diagnostic tool, which analyzes the
149 protein composition of a bacterial cell and help in identification of species[7].
150 However, additional spectral databases has to be included for identification of

151 *Nocardia* on the MALDI TOF, the species confirmation warrants 16S rRNA genetic
152 sequencing.

153 The signs and symptoms of *Nocardia* mimic conditions like tuberculosis, fungal
154 pneumonia or lung cancer, hence it should be always considered as a differential
155 diagnosis in immunocompromised patients when they do not respond to standard
156 treatment.[8]

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

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

168 The standard treatment of nocardiosis is usually a sulfa-containing regimen, but
169 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. otitisdiscaaiarium* 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].

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.

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Fig.1. Cutaneous wheal lesions in disseminated Nocardiosis

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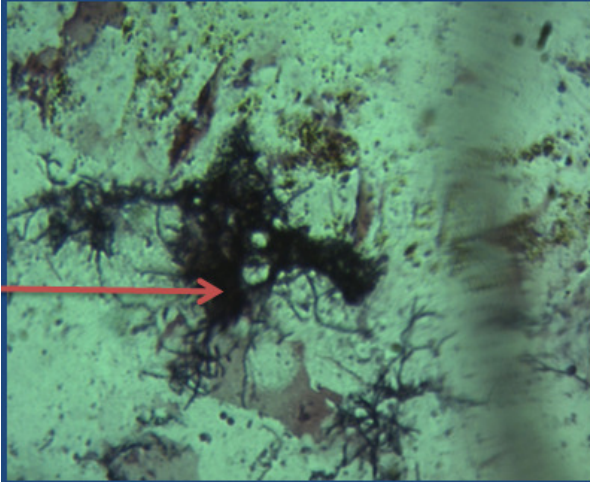


Fig 2a. Gram stain showing branching Gram positive filaments

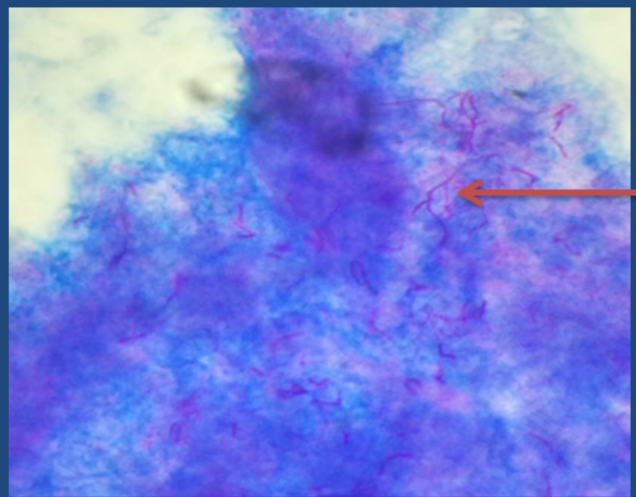


Fig .2b. 1% Acid fast stain showing partially acid fast branching filaments

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