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Nocardiosis: Case Series in a Tertiary Care Center in Central Kerala

Authors
Dr Chris Mary Antony[1], Dr Kiran Jose[2], Dr Tanya Tony Mampilly[3], Dr Vibi Varghese[4], Dr Neethu John[5], Dr Aswathy Varghese[6], Dr Anu Mary Antony[7]
Department of Microbiology, Govt. Medical College, Ernakulam, Kerala
*Corresponding Author
Dr Lancy Justus
Professor of Microbiology, Govt. Medical College, Ernakulam

Abstract
Nocardiosis is a localised or disseminated opportunistic infection caused by an aerobic gram positive filamentous organism that usually affects immunocompromised individuals. There are more than 100 species of nocardia identified with more than 30 species causing clinical disease in humans. It is a rare opportunistic infection. We are reporting 4 cases of nocardiosis diagnosed with laboratory confirmation including species identification at Govt. Medical College, Ernakulam within a short period of 6 months from August 2019 to January 2020.One case of pulmonary nocardiosis from which Nocardia farcinica was isolated from sputum sample. Another was a case of disseminated nocardiosis and the isolate was obtained from blood sample. Third one was a HIV positive patient with axillary abscess from whom Nocardia brasiliensis was isolated from aspirated pus sample. Fourth one was a patient with soft tissue infection from whom Nocardia cyriacigeorgia was isolated from the aspirated pus sample. All the isolates obtained from culture of the clinical samples were confirmed with Vitek-2 and species identification was made by MALDI-TOF. All the four patients had undergone parenteral administration of combination therapy with Ceftriaxone, Amikacin and IMIpenem followed by oral Co-trimoxazole. Three patients survived and one patient with disseminated nocardiosis expired after 1 month inspite of effective treatment with several antibiotics.
Keywords: *Nocardia species nocardiosis, immunocompromised individual.*

Introduction

Nocardia species are ubiquitous soil saprophytes which cause opportunistic infection usually in immunocompromised individuals such as patients with malignancies, transplant recipients, patients on prolonged steroid therapy, HIV infected patients and patients with leucocyte deficiencies. Pulmonary disease is the most common presentation in which route of infection will be by inhalation Extra pulmonary disease may be presented as skin and soft tissue infection and CNS infection. Direct inoculation of the organism through occupational exposure may lead to primary cutaneous nocardiosis which is also more frequently observed. Isolation of the organism from clinical specimens does not always indicate infection. It may be a colonization of the skin and upper respiratory tract or laboratory contamination both the clinical as well as laboratory diagnosis may be challenging as signs and symptoms are not specific and necessity for the correlation of the clinical isolate.

Description of Cases

Case 1: A 54 year old male was admitted in the Medical ICU of GMC, Ernakulam on 21/08/2019 in a stuporous condition. He was admitted at general hospital, Ernakulam one month ago and was treated for nocardial skin abscess. He was diagnosed with pulmonary tuberculosis. 3 years ago and was on ATT for 4 months only. His chest x-ray showed bilateral hilar shadows and his CT chest showed mass lesion in the right middle lobe. He was advised CT guided FNAC, which was done at Govt. Medical College, Kottayam. Pus sample was positive for Acid fast bacilli. The patient was started on ATT and sent back to GMC, Ernakulam. Provisional diagnosis was made as reactivation of pulmonary tuberculosis. Blood sample sent for culture and sensitivity yielded gram positive branching filamentous bacilli. Modified Acid –fast staining yielded branching filamentous acid-fast bacilli. Presumptive identification made was nocardia species and confirmation of the isolate by vitek -2 compact at Malabar cancer center on 14/09/2019. Organism was identified as Nocardia farcinica. Patient was started on ceftriaxone followed by streptomycin, co-trimoxazole doxycycline and moxifloxacin. At the initial stages, he was improved but later his condition worsened and he expired on 11/09/2019.

Case 2: A 75-year-old male brought to the outpatient department of Medicine at GMC, Ernakulam on 29/09/2019 with fatigue and disorientation. He was referred from General Hospital, Ernakulam suspecting hyponatremia and for the management of the same. He had loose stools and vomiting for 4 days. He had past H/O pulmonary tuberculosis 10 years back and completed ATT. Now he has developed cough and breathlessness for the last 2 weeks. He was a case of CAD, COPD, CKD and Hypertension. He had a breast lump of 5X3 cm size hard in consistency. Aspirate from the breast lump was sent for cytology and report showed carcinomatous changes. Sputum for culture and sensitivity was received in the Microbiology Laboratory, at GMC, Ernakulam on 02/10/2019. After 72 hours of incubation the growth was identified as Nocardia species and confirmed with vitek -2. Species identification was made by MALDI-TOF as Nocardia cyriacigeorgica. Patient was treated with ceftriaxone and IV fluids. He was discharged at request on 05/10/2019 for further management of carcinoma breast.

Case 3: A 47 old male, HIV positive patient on ART attended the outpatient department of Medicine on 04/10/2019 with painful soft swelling in the right axilla of 3 days duration. Clinical diagnosis was made as axillary abscess. Incision and drainage was done and 50ml of thick purulent pus was aspirated and sent for culture and sensitivity. He was given combination therapy with cefotriaxone and Imipenemand followed by oral Co-trimoxazole.. After 72 hours of incubation, culture yielded Gram positive bacilli morphologically resembling nocardiaspecies. Identification of the isolate was confirmed with vitek -2 and species identified as Nocrdia brasiliensis by MALDI – TOF. Patient was treated with Amikacin and Imipenem for 1 week and discharged with oral Co-trimoxazole for 3 months.

Case 4: A 67 year old male who was attending outpatient Department of Pulmonary Medicine at Govt. Medical College, Ernakulam came on 2/1/2020 with H/O cough, breathlessness for 1 week duration. Patient was an old case of pulmonary tuberculosis on ATT for one year. Sputum was sent for culture and sensitivity. Modified acid fast staining with 1% sulphuric acid showed, thin long filamentous acid fast bacilli in groups. Culture yielded Nocardia farcinica confirmed by Vitek-2. Patient was treated with amikacin and Imipenem for 3 weeks and discharged with oral administration of co-trimoxazole for 3 months. Patient was better after treatment.

	CASE 1	CASE 2	CASE 3	CASE 4
Date	22.08.2019	02.10.2019	04.10.2019	02.01.2020
Sample	Blood	Exudate	Exudate	Sputum
Clinical diagnosis	Disseminated nocardiosis	Soft tissue infection	Axillary abscess	Pulmonary nocardiosis
Species identified	Nocardiafarcinica	Nocardiacyriacigeorgica	Norcardiabrasiliensis	Norcardiafarcinica
Antibiotic sensitivity	Amikacin, ciprofloxacin Imipenem, meropenem Ceftriaxone, doxycycline linezolid	Ceftriaxone amikacin linezolid	Amikacin, ciprofloxacin Imipenem, meropenem Linezolid Co-trimoxazole	Amikacin, Imipenem, meropenem Linezolid Co-trimoxazole
Resistance	Tobramycin Gentamicin Co-trimoxazole	Ciprofloxacin Gentamicin Co-trimoxazole Imipenem, meropenem	Cefotaxime Ceftriaxone Tobramycin Gentamicin	Cefotaxime Ceftriaxone Tobramycin Gentamicin ciprofloxacin
Treated with	Ceftriaxone+Amikacin, + Doxycycline	Ceftriaxone + Amikacin,	Imipenem, +Amikacin+ Co-trimoxazole	Ceftriaxone+ Imipenem + Co-trimoxazole
Duration of treatment	Combination therapy 3 week	Parenteral three week and discharged at request	Parenteral threeweeks followed by oral co-trimoxazole 12 weeks	Parenteral threeweeks followed by oral co-trimoxazole 12 weeks
Outcome	Expired	survived	survived	survived

Laboratory Diagnosis

Samples were collected for isolation of nocardia species based on the clinical type of infection. In the case of pulmonary infection, sputum sample was collected and in extra pulmonary infections especially in cases of axillary abscess and soft tissue infection, pus samples were collected. In cases of disseminated infections, blood sample was collected. All the 4 samples were sent to the Bacteriology laboratory of the Department of Microbiology, Govt Medical College, Ernakulam immediately after collection.

Laboratory Procedures

Staining

Gram staining done on the smears prepared from sputum and pus samples showed thin, branching, filamentous, Gram positive bacilli along with pus cells.

Modified acid fast staining with 1% sulphuric acid showed, thin long filamentous acid fast bacilli in groups.

Culture

Samples were inoculated onto Blood agar, chocolate agar and MacConkey agar. After 72 hrs of incubation, Blood agar and chocolate agar showed white, wrinkled, velvety colonies. MacConkey agar showed no growth. Suspected colonies were subcultured onto Blood agar plate for pure growth and it was sent for Vitek-2 and MALDI-TOF for confirmation.

Biochemical Reactions

Catalase - Positive
Casein hydrolysis - Positive
L-Tyrosine hydrolysis - Positive
Xanthine hydrolysis - Positive

Antibiotic Sensitivity Testing

Anitibiotic sensitivity testing was performed by Modified disk-diffusion method. All the isolates were sensitive to Amikacin, Imipenem, Meropenem, Ceftriaxone and Linezolid. 50% of isolates were sensitive to ciprofloxacin and Co-trimoxazole. All the isolates were resistant to Gentamicin, Tobramycin and Ampicillin. 50% of the isolates were resistant to Ciprofloxacin, Co-trimoxazole and Ampicillin- Clavulanic acid.

Discussion

Nocardia species are can cause serious and life threatening infections in the immunocompromised

hosts. The route of infection can be either by inhalation or by direct cutaneous inoculation.

Predisposing Factors

Being an opportunistic infection, Nocardiosis is seen particularly in patients with lymphoreticular neoplasms. There are many predisposing factors such as impaired local pulmonary defenses, therapy with cytotoxic drugs alone or in combinatyion with steroids and any condition requiring long term administration of corticosteroids. Systemic immunosuppression particularly CMI dysfunction predisposes to the evolution of invasive pulmonary nocardiosis seen frequently in renal, cardiac and liver transplant recepients. Nocardial pneumonia also occurs without concurrent diseases or therapies. The reported prevalence usually ranges from 10% to 25%. Invasive nocardial infections account for 4% of infections in patients following renal transplantation. The use of cyclosporine has notably decreased the incidence of nocardial infections in both renal and cardiac transplantation patients.

Pulmonary Nocardiosis

Lungs are the most common site of involvement and are affected in 70% of all cases of nocardiosis. Pulmonary nocardiosis is an acute, subacute or chronic suppurative infection with a pronounced tendency to remissions and exacerbations. The most common initial diagnosis may be pneumonia. Later it may be tuberculosis, mycosis, carcinoma, lung abscess. Nothing in the clinical or radiographic presentation of pulmonary nocardiosis is sufficiently distinctive to be diagnostic. Clinical manifestations are variable and in no way specific.

Chronic lung disease continues to be significant predisposing condition for invasive nocardiosis. COPD has been found as a predisposing factor in 23-70% of pulmonary nocardiosis.

Systemic and Extra Pulmonary Nocardiosis

Primary nocardial infection, either from the lungs or from posttraumatic skin and soft tissue inoculation may erode into blood vessels or spread hematogenously. The presence of lesions in 2 or more organs of the body defines systemic or disseminated disease. The most common sites for disseminations include the CNS (brain), skin and subcutaneous tissues and heart. In systemic infection, Nocardia behave as pyogenic bacteria during early stages of the infection. A granulomatous picture, as seen with Mycobacterium tuberculosis infections can be found in infection with some nocardial strains, but this type of host response is distinctly uncommon. One of our patients in our report series is a HIV infected patient. Early reports expressed surprise that so few cases of nocardiosis were occurring but it is no longer an uncommon complication of AIDS. Geographic variations may relate the incidence of nocardiosis in patients with AIDS. Advanced HIV infection has become the predominant underlying condition for nocardiosis in some hospitals in United States. The disease is mainly seen among the HIV patients receiving HAART and with less than 100 CD4 T cells/mm^3

Nocardia Bactermia

Although rare, nocardia bacteremia is an important diagnosis due to the specific antimicrobial and supportive management of strategies required for treatment and to high overall all-cause mortality. In a review, it was shown that blood cultures were the only positive microbiological specimens in 385 of cases thus serving as an important and non-invasive diagnostic test for nocardiosis. Immunosuppression and intravascular devices were most commonly associated with nocardia bacteremia. 91% of cases in a case study was having one of these factors.

The overall incidence of nocardiosis in different types of immunosuppressed populations has been estimated as approximately 4%. The mortality rate is approximately 7%. However, very few series reflect the whole spectrum of the disease in all types of patients. Chronic lung disease continued to be a significant predisposing condition for invasive nocardiosis.

The importance of the widespread use of corticosteroids and other immunosuppressive agents has been related to emergence of many opportunistic infections such as nocardiosis. Corticosteroids are indicated to treat an expanding spectrum of diseases including COPD with exacerbations. It is estimated that 62.5% of COPD patients were receiving corticosteroid therapy in a case series study.

Prophylaxis with Co-trimoxazole is recommended in patients with prolonged high dose corticosteroid therapy mainly in non-classic immunocompromised patients but this recommendation is not always followed in daily practice. In a previous study by Maricela Valerio et al, it was reported that among the study population, 62% were receiving corticosteroids but only 21% were on Co-trimoxazole prophylaxis. However, Co-trimoxazole prophylaxis should not be considered a guarantee for absolute protection against nocardiosis.

Antimicrobial Susceptibility Testing and Therapy

It is challenging to review since the antimicrobial susceptibility testing of Nocardia species remains problematic. Testing methids include modified disk- diffusion, agar dilution, broth microdilution and radiometric growth index. Co-trimoxazole is the frequently used oral drug to treat nocardiosis despite the absence of conclusive data supporting the need for combination therapy. The potential drugs like Amikacin, Imipenem, are 90% active against Nocardia species and reduces mortality rate. Varying combinations of Amikacin and Imipenem with Cefotaxime and Co-trimoxazole display in vitro synergy. Most of the species of nocardia respond to this combination therapy very well. In our study, all the isolates are resistant to Ampicillin, Cefixime, tobramycin and 50% of the isolates were resistant to Ciprofloxacin and Ampicillin-clavulanic acid. Optimal duration of therapy is uncertain but long term therapy, usually more than 3 months is recommended because nocardial infections tend to relapse.

Conclusion

Nocardiosis is still a rare opportunistic infection mainly affecting the immunocompromised population usually presenting in a diverse clinical picture with significant morbidity and mortality. The incidence of the infection is increasing due to increase in number of patients receiving immunosuppressive agents for organ transplantation and malignancies. Although Nocardia species are capable of producing serious infections, early diagnosis and initiation of appropriate treatment in the early phase of the disease can lead to successful outcome. Most of the patients survive the infection. Delay in diagnosis and early suspension of treatment especially in AIDS patients can lead to relapse due to treatment failure

Abbreviations

COPD- Chronic Obstructive Pulmonary Disease
AIDS- Acquired Immuno Deficiency Syndrome
MALDI-TOF- Matrix Associated Laser Desorption/ Ionisation – Time of Flight.

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Conflicts of Interest

There are no conflicts of interest to declare

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