

Case Series

Clinical spectrum and outcome of nocardiosis in Oman: a case series from a single center

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ABSTRACT

Nocardiosis is an opportunistic bacterial infection caused by aerobic Gram-positive bacteria belonging to the actinomycetes group. With the increase in the population of immunocompromised patients, these infections have been identified in the middle east countries. In a retrospective study of 13 years, we found ten patients who were culture confirmed nocardiosis. Among this series, pulmonary nocardiosis predominated with 80%. Most of the species of *Nocardia* were identified using the molecular testing, 16S rRNA gene sequencing and drug susceptibilities were performed in 70% and 60% respectively. Treatment is usually based on susceptibility testing which give a better clinical cure and outcome. Cotrimoxazole formed the back bone of the treatment. Although, small in number, this case series is the largest reported from the any middle east country and it can assist the clinicians with high clinical suspicion of infection and early treatment.

Keywords: Nocardiosis, *Nocardia* spp, Chronic lung disease, 16sRNA, Culture confirmed nocardiosis, Oman

INTRODUCTION

Nocardiosis is a bacterial infection caused by aerobic Gram-positive bacteria belonging to the actinomycetes group. It can cause a wide spectrum of disease immunocompromised as well as immunocompetent hosts.

In the recent years, there have been a rise in the cases of *Nocardia* infection worldwide.¹ This can be attributed to the increasing number of immunocompromised individuals. Nocardiosis can also been seen in the immunocompetent host, mainly causing a localized disease but disseminated infections have been reported.²

Nocardia is a ubiquitous saprophyte commonly found on the decomposing plant material, soil and air. The distribution of *Nocardia* infection differs according to the regions, climatic conditions and temperatures. A few studies, by Peleg and a study from Quebec, demonstrated

a prevalence rate of 0.6% among the transplant recipients and an annual incidence of 0.87% respectively.^{3,4}

From the middle eastern countries, there are a couple of case series published from Saudi Arabia.^{5,6}

Nocardia is a thin branching filamentous Gram-positive, partially acid-fast, catalase positive aerobic bacteria belonging to the class actinomycetes. Difficulty on isolation of *Nocardia* from the traditional culture methods may result in under diagnosing and thus under reporting of cases.

Accurate identification of the organism, its speciation and drug susceptibility testing are paramount to successful treatment of the infection caused by *Nocardia*. Molecular identification has led to the validation of newer species of *Nocardia*.⁷ Newer methods, like Gene sequencing, multi locus sequence typing (MLST) and whole genome sequencing (WGS) may be used for identification of the

species of *Nocardia*.⁸ Identification of genus *Nocardia* can be performed directly on the agar plate by using MALDI - ToF or 16S rRNA sequencing.⁹

Drug susceptibility testing for *Nocardia* isolates is an important step in the treatment of the infection. Antibiotic susceptibility testing is performed as per the CLSI (Clinical and laboratory standard institutes) guidelines.¹⁰

In a publication by Brown et al in the US population, majority of the *Nocardia* infections are seen in dry, warm and windy climates. This type of climatic conditions exists in the middle east countries.¹¹

Inhalation is the primary source of acquisition of the disease-causing primary lung infection.¹² Direct inoculation of the organism primarily causes cutaneous diseases and is seen due to traumatic injury like a prick from plants or wood.¹³ Deeper infections like septic arthritis and road traffic accidents causing a severe infection like meningitis after traumatic skull fracture are also seen with *Nocardia* infections.¹⁴

Disseminated disease due to hematogenous spread is usually seen in immunocompromised individuals and the risk is highest amongst the transplant recipients.¹⁵ In a large multicentric study, 42.7% of the patients were reported to have a disseminated disease.⁷

In pulmonary disease the most common mode of presentation is cough and dyspnea and fever.¹⁶ Pleuritic chest pains can also be a symptom with the involvement of the pleura, 20-40% of the immunocompromised individuals are colonized with *Nocardia* and they are usually asymptomatic.¹⁷

Primary cutaneous disease is a result of inoculation and hence presents as ulcers, cutaneous abscesses, granulomas as well as cellulitis.¹⁸ About a third of the patients can have lymphocutaneous spread involving the regional lymphatics and is called sporotrichoid nocardiosis as it mimics sporotrichosis.¹⁷ Other differential diagnosis to be considered in an individual presenting with cutaneous disease is *Mycobacterium marinum* infection.¹⁹

Disseminated disease is due to hematogenous spread can cause deeper tissue involvement. It is more common in the immunocompromised individuals and CNS can get involved in even asymptomatic patients.²⁰ Hence radiological screening (CT or MRI) is recommended in all immunocompromised patients with suspected *Nocardia* infection.²¹

Treatment for *Nocardia* depends on the form of infection and its severity. Individualization of treatment based on the species identification and drug susceptibility forms an important basis for successful outcome.²² For severe infections, empiric multidrug therapy can be initiated with broad spectrum like, carbapenems (meropenem or imipenem), trimethoprim-sulfamethoxazole (TMP-SMX),

amikacin, linezolid and cephalosporins (ceftriaxone).²³ While dealing with CNS infections, care should be taken to use drugs with better penetration to the CNS.²⁴

Outcome of patients with early diagnosis and appropriate treatment is generally excellent. Species identification and drug susceptibility play a major role in a good prognosis.²⁵

Hence this study was planned to better understand the clinical profile, risk factors, modalities of diagnosis, treatment and outcome in Oman.

CASE SERIES

During the study period of 13 years, 10 cases of culture confirmed Nocardiosis were identified, and the details of the patients are as follows:

Patient 1

A 46-year-old man, from Al-Batinah governorate of Oman is a case of chronic myeloid leukemia underwent hematopoietic bone marrow transplant. A year after the transplant, he presented with lower limb weakness. He was diagnosed to have brain abscess for which he underwent craniotomy and the tissue culture sent for culture grew *Nocardia sp.* He also had lung involvement for which bronchoscopy was done and the broncho alveolar lavage grew *Nocardia*. He has disseminated disease involving the brain and the lung. His risk factors were hematological malignancy and bone marrow transplant requiring immunosuppression. The isolate of *Nocardia* was not speciated but drug susceptibility was done as shown in the table (Table 1). He was started on IV meropenem, amikacin and linezolid for the initiation 2 weeks followed by oral cotrimoxazole and linezolid and IV meropenem was continued for 6 weeks. Oral therapy with cotrimoxazole and linezolid was continued for 12 months of duration. The patient remains well.

Patient 2

A 28-year-old man who was from Al-Sharqiyah, a case of pre-B cell ALL underwent hematopoietic bone marrow transplant. 9 months after the transplant he developed graft versus host disease (GVHD) involving the skin and the lungs requiring triple immunosuppression. He presented with worsening respiratory symptoms. CT chest was suggestive of chronic destroyed lung with new patchy consolidation. He underwent bronchoscopy and *Nocardia* was isolated from the broncho alveolar lavage culture. His risk factors included hematological malignancy, bone marrow transplantation and GVHD involving the lungs requiring heavy immunosuppression and an underlying lung involvement. The isolate was identified as *Nocardia crassostreas* by 16S rRNA gene sequencing and drug susceptibility was performed as shown in table (Table 1). He also had co-infection with *Mycobacterium abscesses*. He was treated with multiple combination of drugs like meropenem, amikacin, linezolid, clarithromycin and

moxifloxacin. He is still on treatment and his lung function remains poor.

Patient 3

A 69-year-old woman who was from Ash-Sharqiyah, presented in acute and severe respiratory failure was admitted in the intensive care unit requiring high ventilatory support. There was a history of trauma to the right thumb ten days prior to the presentation. Her sputum and broncho alveolar lavage grew *Nocardia sp.* in culture. She had an acute infection involving the lungs and trauma to the extremity was considered a site of inoculation. The isolate was speciated as *Nocardia otitidiscaviarum* but drug susceptibility could not be performed. She was initiated on IV meropenem plus amikacin and cotrimoxazole. She rapidly went into severe ARDS and died.

Patient 4

A 44-year-old woman from Al-Dakhiliyah, who was a diagnosed case of systemic lupus erythromatosus (SLE) with lupus nephritis causing end-stage kidney disease on triple immunosuppression presented with pneumonia and pleural effusion. Pleural fluid aspirate was sent for culture and it isolated *Nocardia sp.* Her risk factor included immunosuppression for SLE and the organ of involvement was lung. The isolated species was identified as *Nocardia cyriacigeorgica* by using 16S rRNA gene sequencing but drug susceptibility could not be performed. She improved initially on treatment and was discharged but soon readmitted due to CMV disease and died.

Patient 5

A 60-year-old man from Barka, a coastal city in a region Al Batinah, with background of diabetes mellitus, hypertension, IV drug abuse, smoker and ethanol consumer was admitted with hemiplegia and was found to have brain abscess on neuro imaging. He underwent craniotomy and abscess evacuation. The culture from the brain tissue sent intra-operatively grew *Nocardia sp.* So, he had multiple risk factors and had central nervous system (CNS) involvement. The isolate could not be speciated, but drug susceptibility was done for the isolate as shown in the table (Table 1). The treatment given to him was IV meropenem. IV Amikacin and cotrimoxazole for 2 weeks which was followed by oral linezolid and ciprofloxacin. This patient died due to dys-electrolytemia and we believe, it was not directly related to Nocardiosis.

Patient 6

A 2.5-year-old boy from Bowshar, Muscat governate of Oman with underlying chronic granulomatous disease on prophylaxis with Cotrimoxazole and Itraconazole presented with 4 days history of fever and abscess in the right scapular area. He underwent incision and drainage and the pus culture isolated *Nocardia sp.* So, he had a

breakthrough infection while he was on prophylaxis with cotrimoxazole. This isolate was speciated using MALDY-TOF and was confirmed by molecular test 16S rRNA gene sequencing as *Nocardia cyriacigeorgica*. Drug susceptibility was done as shown in the table (Table 1). The patient received 2 weeks of IV meropenem and IV linezolid followed by oral linezolid for 4 weeks.

Patient 7

A 27-year-old woman from Al-Batinah region of Oman with background illness of systemic lupus erythromatosus (SLE) on immunosuppression presented with history of 2 days duration of fever, headache and vomiting. Had brain abscess in the right parietal region on neuro imaging. She underwent craniotomy and evacuation. The intra-operative brain tissue grew *Nocardia sp.* This isolate could not be speciated but drug susceptibility was done for this isolate as shown in the table (Table 1). She was treated with IV meropenem, IV cotrimoxazole and IV amikacin. Despite of appropriate treatment and surgical evacuation, she had increased intra-cranial pressure and declared brain dead.

Patient 8

A 38-year-old woman from Al-Batinah, with the background illness of bronchiectasis was admitted with worsening respiratory symptoms. She was also a case of congenital neutropenia and had undergone bone marrow transplant 12 years ago and was off any immunosuppressive agents. She underwent bronchoscopy and broncho-alveolar lavage isolated *Nocardia sp.* The species of *Nocardia* was isolated by using 16S rRNA gene sequencing and it was identified as *Nocardia beijingensis/asteroides/ pneumoniae*. This isolate underwent drug susceptibility. She was a case of chronic lung disease, and she had pulmonary nocardiosis. She was initiated on IV cotrimoxazole but was changed to oral doxycycline due to skin allergy to Sulpha drug. She completed 6 months of therapy.

Patient 9

A 51-year-old man from Sur region of Oman with a background of diabetes mellitus and was on steroids for Bell's Palsy with underlying bronchiectasis was admitted with fever and worsening cough. He underwent bronchoscopy and BAL sample grew *Nocardia sp.* This isolate was identified as *Nocardia otitidiscaviarum* by the molecular testing 16S rRNA gene sequencing. Drug susceptibility was not performed on this isolate. So, he had multiple risk factor and had pulmonary nocardiosis. He received IV meropenem and IV cotrimoxazole for 2 weeks which was followed by oral cotrimoxazole for 6 months duration. He is well and is on regular clinic follow up.

Patient 10

A 92-year-old man from Al-Mudhaibi province belonging to Ash-Sharqiyah governorate of Oman, with an

underlying disease of pulmonary fibrosis, emphysema and pulmonary hypertension was admitted with worsening respiratory symptoms. His CT chest revealed right middle lobe mass for which he underwent bronchoscopy and BAL

culture grew *Nocardia sp.* The organism was identified by 16S rRNA gene sequencing as *Nocardia amamiensis*. He was initiated on IV meropenem and IV cotrimoxazole. He died due his poor underlying cardiac and pulmonary status.

Table 1: Drug susceptibility profile of the *Nocardia* isolates in the study.

Drugs	Patient 1, M/46 (Not speciated)	Patient 2, M/28 (<i>Nocardia crassostreae</i>)	Patient 5, M/60 (Not speciated)	Patient 6, 2.5/M (<i>Nocardia cyriageorgica</i>)	Patient 7, 27/M (Not speciated)	Patient 8, F/38 (<i>N. beijingensis/ asteroides/ pneumoniae</i>)
Amoxicillin/ clavulanate	-	I	-	-	S	S
Amikacin	-	R	S	S	S	S
Ciprofloxacin	R	R	S	S	S	R
Clarithromycin	-	R	-	-	-	R
Ceftriaxone	-	R	R	R	S	S
Doxycycline	-	R	-	-	-	S
Imipenem	R	R	-	-	S	R
Linezolid	S	S	S	S	S	S
Moxifloxacin	-	I	-	-	-	R
Tobramycin	-	R	-	-	-	S
Trimethoprim/ sulfamethoxazole	R	R	R	R	R	S
Ceftazidime	-	-	-	-	R	-
Clindamycin	R	-	-	-	R	-
Erythromycin	R	-	-	-	R	-
Gentamicin	R	-	-	-	R	-
Meropenem	-	-	R	S	S	-
Penicillin	R	-	-	-	R	-
Tetracycline	R	-	-	-	S	-
Tigecycline	-	-	-	-	R	-
Minocycline	-	R	-	-	-	-
Ampicillin	R	-	-	R	-	-
Cefuroxime	R	-	-	R	-	-
Rifampicin	R	-	-	R	-	-
Teicoplanin	S	-	-	S	-	-
Vancomycin	R	-	-	R	-	-

*S=sensitive, R=resistant, I=intermediate

DISCUSSION

Nocardiosis is identified as an emerging opportunistic pathogen seen in the immunocompromised individuals. This study provides a series of cases showing the demographic pattern, clinical presentation, risk factors, treatment options and outcome of the patients from the Sultanate of Oman.

During the study period, there were 10 culture confirmed cases of *Nocardia* which were included in this case series. The mode of this soil-borne opportunistic infection is primarily inhalational and a small proportion may be due to direct inoculation. This makes chronic lung disease a very important risk factors for the acquisition of disease. The pathogen gets lodged into lung which is diseased.

A study conducted in a single center in Brazil, demonstrated diabetes mellitus as the most common risk factors (50%) followed by chronic lung disease in the 33.3%.²⁶

A study conducted amongst patients receiving immunosuppressants after organ transplant, 57% were receiving these drugs (steroids, calcineurin inhibitors, mycophenolate mofetil, infliximab or antimetabolites) for more than three months and 37% were receiving a combination of the drugs compared to 20 patients who were on monotherapy.²⁷

The taxonomy of the genus *Nocardia* is very conflicting, and the species involved in causing human disease continue to emerge. As a result, it has a serious implication

on the treatment. Due to epidemiological variation and varied clinical presentation, from localized form to a disseminated disease, the treatment options should be carefully chosen based on the species identification and drug susceptibilities.²⁸

In this study, in spite of using molecular methods, not all isolates could be speciated. A study conducted by Couble et al the authors were able to detect 5 species of *Nocardia* directly from 18 clinical samples using molecular methods.⁸

Due to lack of standard treatment, it is best to treat according to the drug susceptibility, if available. Trimethoprim-sulfamethoxazole forms the first line of therapy in most of the cases, however parenteral, good bioavailability and CNS penetration of the drug is preferred while treating severe forms and CNS involvement.

Drugs like, linezolid and amikacin performed the best across all species. Hence linezolid was used in combination with the other susceptible agent in most of our patients. However, due to adverse effects of bone marrow suppression, it becomes a difficult choice in patients who are already cytopenic due to underlying disease or chemotherapy-induced.

In our study, out of the 6 isolates where drug susceptibility was performed, 5 isolates were resistant to sulfamethoxazole-trimethoprim (TMP-SMX). This was in contrast to a multicentric study conducted by Brown et al where TMP-SMX was found to be susceptible.²⁹ In another study, 90% curative rate was seen in patients treated with TMP-SMX alone or in combination.⁵

In this case series of 10 patients, five of them died. In two of the patients, the mortality was not attributed to *Nocardia* infection. Waheba et al reported a mortality rate of 8.6% in a study from a transplant center in Saudi Arabia.⁵ In a similar single center study, Bruno et al reported an overall case fatality of 33.3% and higher of 66.7% in patients with disseminated nocardiosis.²⁶

In our study, treatment related adverse event was seen in only one patient, which was intolerance to medications. Since the treatment duration is 6 months or more, adverse events should be kept on mind specially while using TMP-SMX, linezolid and amikacin.

CONCLUSION

With the increasing population of immunocompromised individuals in the Sultanate of Oman and the presence of *Nocardia* infection, a high degree of clinical suspicion is required. Discussion with the microbiological colleagues will lead to early diagnosis. Molecular testing could be facilitated earlier if the routine cultures remain negative. Species identification and drug susceptibility remains an important pillar in initiating appropriate treatment and

better outcomes. Although a small number of cases, we believe it's important to highlight the presence of *Nocardia* in the region of Oman and more collaborative efforts will lead to better outcomes.

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