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A ten-year retrospective analysis of nocardiosis in a tertiary care center of South-coastal India

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SUMMARY

Nocardiosis is an uncommon life-threatening infection caused by *Nocardia* spp. This study aimed to review the distribution of risk factors, clinical characteristics, microbiological findings, treatment and outcome of patients diagnosed with nocardiosis. This study was a retrospective case record review of all nocardiosis cases that were diagnosed at our tertiary care hospital from January 2008 to December 2019. A total of 48 patients with a mean age of 52.2±16.28 years were included. Out of which forty one (85%) were diagnosed as pulmonary nocardiosis and seven (14.6%) as disseminated disease. Chronic lung disease 25 (52.1%), long term steroid use 22 (45.8%) followed by diabetes mellitus 11 (22.9%) were common predisposing factors. The common symptoms were fever (87.5%), cough (79.2%) and breathlessness (52.1%). The most frequent radiologic finding included consolidation in 38 (79.1%), cavitation with thickened wall in 2 (4.1%), reticulonodular shadows in 2 (4.1%), and unilateral pleural effusion in 5 (10.4%). *Nocardia otitidiscaviarum* (22.9%) was frequently isolated from cultures. Resistance to trimethoprim-sulfamethoxazole (TMP-SMX) was observed in 21% cases. Mortality was noted in 6 (12.5%) patients and all were with pulmonary involvement. The percentage of death among those with and without pulmonary tuberculosis was 33.3% and 5% respectively. Patients affected by pulmonary nocardiosis with previous history of pulmonary tuberculosis showed significant association with poor outcome (p-value=0.05). In conclusion, nocardiosis mainly affects patients with structural lung disease or immunocompromised hosts with adverse outcome. Awareness of this infection is crucial for a clinician, and any suspicion should lead to make an early diagnosis and choose an appropriate empirical treatment to improve the outcome in this population.

Keywords: *Nocardia* spp., immunocompromised, pulmonary nocardiosis.

INTRODUCTION

Nocardia is an aerobic Gram-positive filamentous bacteria, ubiquitous in distribution. It is a saprophytic organism found in soil mainly rich in organic matters. The infection spreads by inhalation of bacteria when soil is disturbed by human activities [1, 2]. It is an opportunistic pathogen with low virulence but causes serious complications in delayed diagnosis and immunocompromised patients [3]. Pulmonary, lymphocutaneous, cardiac, ocular, neurological forms are the commonly reported manifestations of nocardiosis [4]. In recent decade, the nocardiosis cases have increased and mainly reported in patients with

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renal failure, bone marrow transplantation, use of corticosteroids, AIDS, and patients under chemotherapy [4]. Most common species of Nocardia associated with infections includes *Nocardia asteroids, Nocardia brasiliensis, Nocardia farcinica* and *Nocardia nova*, whereas *Nocardia otitidiscaviarum* and *Nocardia pseudobrasiliensis* are less commonly reported. All the etiological agents of nocardiosis are not well established and different species are reported more in different forms of infections [5]. *Nocardia elegans* has recently been reported in less than 1% of cases of disseminated nocardiosis [6]. The mechanism of host-parasitic relationship in nocardiosis is not completely understood and the clinical presentation varies in different cases [7]. *Aspergillus* spp. (12.5%), cytomegalovirus (CMV) (18.8%) or mycobacterium (25%) are the associated co-infections reported with nocardiosis [8, 9].

There has been a recent upsurge of nocardiosis among the Indian population. Immunosuppressive etiology, such as cancer, solid organ transplantation, autoimmune diseases, use of steroids, and immunosuppressive drugs, were shown to be risk factors in the majority of patients (11 out of 13 diagnosed) in an Indian population [10]. The clinical presentation of patients with nocardiosis is not well studied and it mimics actinomycosis, tuberculosis, cryptococcosis and toxoplasmosis [10]. Due to non-specific clinical presentation and variety of differential diagnosis with same manifestations, it is often missed, delayed, or misdiagnosed leading to poor prognosis and inappropriate empirical therapy complicating the management of infection in patients. We aim to study demography, distribution of risk factors, clinical characteristics, laboratory findings, treatment and outcome of nocardial infection in our tertiary care hospital in Southern India.

PATIENTS AND METHODS

Patients and setting

This retrospective study was carried out in a tertiary care teaching hospital in South India from January 2008 to December 2019. Patients aged 18 years or older with a microbiologically confirmed diagnosis and appropriate clinical signs and symptoms were included in the study. Patients with clinically suspected nocardiosis, not confirmed by culture or staining were excluded from the study. The patients' data was collected from the medical records. It included demographics, co-morbidity, clinical course, radiographic presentation, laboratory findings, treatment course and outcome. The study was approved by the Institutional Ethics Committee (IEC number: 376/2019). Written informed consent was waived due to retrospective nature of the analysis.

Definitions

Pulmonary nocardiosis was defined as the presence of clinical symptoms and signs of respiratory infection with nocardia species isolated from respiratory samples, including sputum or bronchoalveolar lavage at least once. Disseminated nocardiosis was diagnosed if the infection was present in two non-contiguous sites with or without a pulmonary focus. Long-term steroid use was defined as patients taking at least 10 mg of prednisolone per day for more than one month before the development of nocardiosis [8].

Microbiological analysis

Various clinical samples of suspected nocardial infection were subjected to Gram staining that revealed many thin, Gram positive, branching filamentous bacteria and then confirmed with modified acid-fast staining (Kinyoun staining) with 1% sulphuric acid that showed partial acid fast filaments. These samples were cultured on 5% sheep blood agar, Sabouraud dextrose agar (SDA) and nutrient agar and incubated aerobically at 37°C under 5% CO_2 for 4 weeks. The dry chalky white colonies suspected of nocardia were confirmed with microscopy and were speciated by using a battery of biochemical tests like urease production, citrate utilisation, and hydrolysis of casein, tyrosine, xanthine and hypoxanthine and examined for growth at 45°C. Antibiotic sensitivity testing was done using disk diffusion method according to the Clinical Laboratory Standards Institute guidelines (CLSI) [11].

Statistical analysis

The distribution of risk factors, clinical characteristics, laboratory findings and treatment details were expressed in terms of frequency and percentages or mean ± SD. The association of various risk factors with the patient outcome was analysed using Fisher exact test. All the data analysis was carried out using R software.

RESULTS

Figure 1 shows the annual percentage of hospitalized cases with nocardiosis diagnosed in a tertiary care teaching hospital between 2008 and 2019. A total of 48 patient's medical records were reviewed. The diagnosis of pulmonary nocardiosis was made in forty one (85%) cases and seven (14.6%) of them had disseminated disease. Within the disseminated disease group, one patient had pericardial effusion with pancreatic abscess, one had bacteremia, two had brain abscess with bacteremia, one patient had pancreatic abscess with paraspinal abscess and one had gross pericardial effusion with empyema. One patient presented with multiple skin ulcers and abscesses in the background of HIV infection and active pulmonary tuberculosis. All patients with disseminated disease had lung involvement except one patient with multiple cutaneous abscesses.

The mean age of presentation was 52.2±16.28 years. The majority of patients were male 33 (68.8%). Chronic lung disease 25 (52.1%) and patients on long-term steroid use 22 (45.8%) followed by diabetes mellitus 11 (22.9%) were the common predisposing factors. Amongst the patients with chronic lung disease, 9 (36%) had chronic obstructive pulmonary disease, 7 (28%) had bronchial asthma, 5 (20%) had old pulmonary tuberculosis with fibrosis as a sequelae and

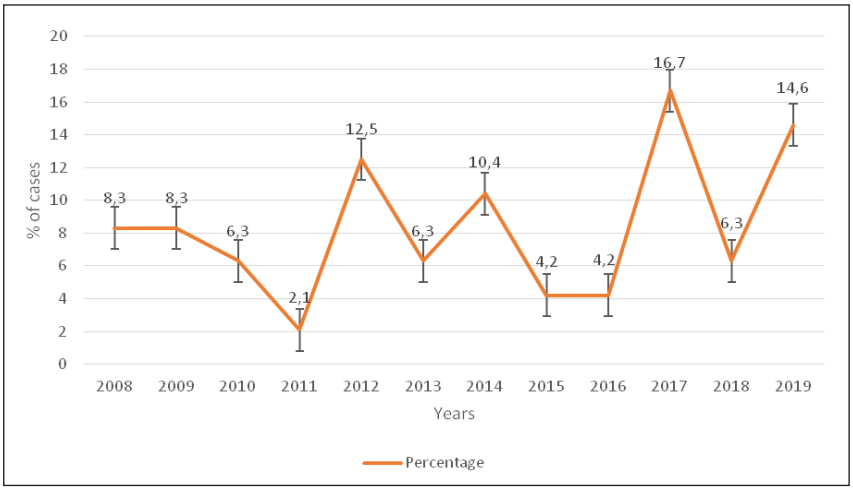

Figure 1 - Yearly percentage (%) of nocardiosis cases diagnosed in the tertiary care hospital between 2008 and 2019.

Table 1 - Demographic characteristics and risk factors for nocardiosis.

Characteristics	*Frequency (n=48)*	*Percentage (%)*
Age, years (mean ± SD)	52.2±16.28	
Gender distribution		
Male	33	68.8
Female	15	31.3
Underlying conditions		
Renal transplantation	5	10.4
Long term corticosteroid use	22	45.8
HIV	7	14.6
Chemotherapy	3	6.3
Diabetes mellitus	11	22.9
Chronic kidney disease	3	6.3
Chronic obstructive pulmonary disease	9	18.8
Bronchial asthma	7	14.6
Pulmonary tuberculosis	12	25
Bronchiectasis	4	8.3

4 (16%) cases had bronchiectasis. In five patients with pulmonary nocardiosis, and in two with disseminated disease, the diagnosis of active pulmonary tuberculosis was made based on sputum smear microscopy and culture or GeneXpert and was started on anti-tubercular therapy in addition to nocardiosis therapy. The demographic and underlying predisposing factors are summarized in Table 1.

Table 2 - Clinico-laboratory and radiological profile of the patients with nocardiosis.

Characteristics	*Frequency (n=48)*	*Percentage (%)*
Fever	42	87.5
Cough	38	79.2
Haemoptysis	6	12.2
Breathlessness	25	52.1
Pleuritic pain	11	22.9
Anorexia	12	25
Weight loss	13	27.1
Skin ulcer/abscess	1	2
Crepitation	23	47.9
Rhonchi	10	20.8
Laboratory findings		
Leukocytosis	33	68.7
Neutrophilia	28	59
Radiographic findings		
Consolidation	38	79.1
Pleural effusion	5	10.4
Empyema	1	2
Reticulonodular shadows	2	4.1
Cavitation	2	4.1
Ring enhancing lesions	2	4.1

Fever was the most consistent complaint 42 (87.5%) followed by cough 38 (79.2%) and breathlessness 25 (52.1%). Increase in white blood cell count (>11,000 cells/mm^3) was noted in 33 (68.7%) cases. The most common radiologic finding was consolidation, which occurred in 38 (79.1%) patients. Cavitation with thickened wall and reticulonodular shadows was detected in 2 (4.1%) patients each in the chest computed tomography (CT). Unilateral pleural effusion was noted in 5 (10.4%) patients. Empyema was noted in one patient with consolidation. Two patients had undergone brain magnetic resonance imaging (MRI) in view of altered sensorium and were found to have a ring-enhancing lesion with surrounding edema. The clinical, laboratory and radiological details are described in Table 2. The typical radiographic findings in our patients with pulmonary nocardiosis are shown in Figure 2.

The diagnosis of nocardiosis was made in 28 patients from the sputum culture while bronchoscopy was needed to establish the diagnosis in 12 patients. *Nocardia* spp. was isolated from the endotracheal tube aspirate culture from three patients who were on ventilator support (Figure 3). In the remaining patients, *Nocardia* spp. was isolated from other samples such as pleural fluid in

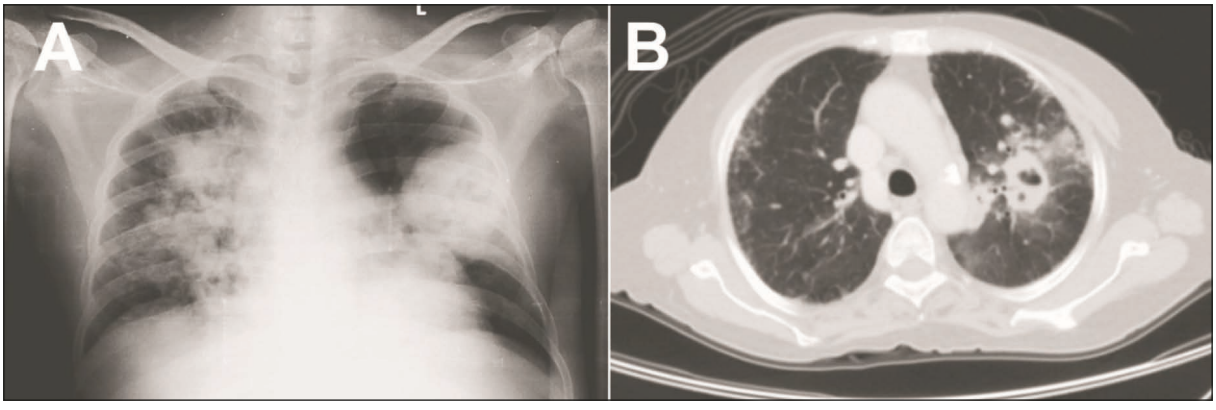

Figure 2 - A. Chest radiograph of a patient on immunosuppressive therapy after renal transplantation infected with *Nocardia* spp. showing patchy consolidation in the right upper, middle and lower zones and in the left middle zone. B. Computed tomography of a patient with bronchial asthma on chronic steroid therapy revealing consolidation with areas of breakdown and air bronchograms in apicoposterior segment of left upper lobe with adjacent areas of ground glass opacification and nodules.

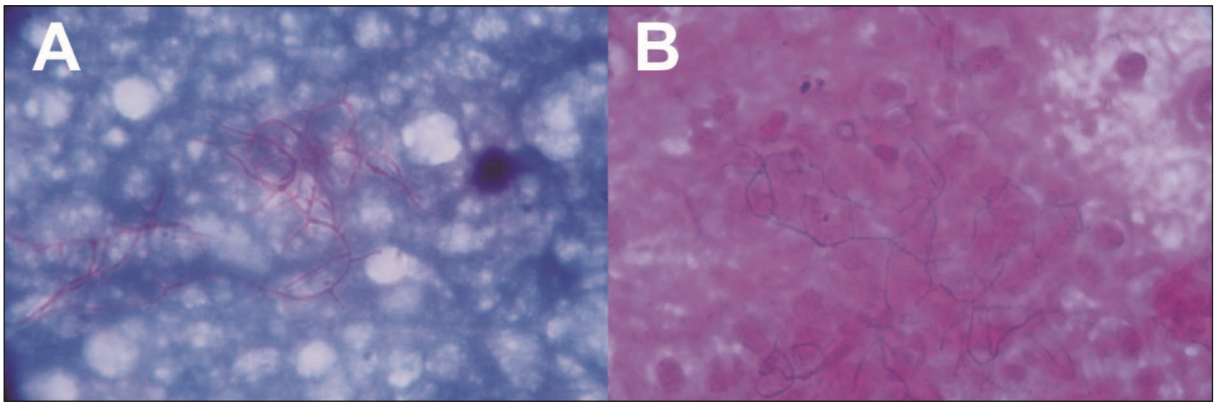

Figure 3 - A. Kinyoun staining showing partial acid-fast filaments; B. Gram staining showing thin, Gram positive, branching filaments suggestive of nocardia.

one patient, brain biopsy in one patient, cutaneous abscess puncture in two patients and blood in 1 patient. *Nocardia otitidiscaviarum* (22.9%) was frequently isolated from cultures and in 62.5% of individuals, *Nocardia* spp. was unidentified from clinical specimens (Table 3).

Treatment and outcome

Most of the patients in the present study received combination therapy except for 6 (12.5%) patients who received monotherapy as a first-line treatment with trimethoprim-sulfamethoxazole (TMP-SMX) at a dose of 10 to 15 mg/kg IV of the trimethoprim component per day in two to three divided doses depending on the severity of infection. Nocardia-specific combination antibiotic regimens included TMP-SMX-ceftriaxone in 12 (25%), TMP-SMX-carbapenem in 12 (25%), TMP-SMX-linezolid in 4 (8.3%), TMP-SMX-amikacin in 5 (10.4%) and TMP-SMX-amikacin-quinolones in 9 (18.8%) patients. None of the patients developed any adverse events during treatment. As the patients' clinical status improved after the first 2 to 4 weeks of therapy, their regimen was changed to oral medication, which was continued for 6 to 12 months. Antibiotic susceptibility report revealed that all nocardia isolates were sensitive to amikacin and linezolid but resistant to ampicillin (87.5%) and amoxicillin/clavulanic acid (82.6%). Resistance to TMP-SMX was observed in 21% cases. Figure 4 shows the antibiotic resistance pattern of all nocardia isolates obtained in this study.

The overall in-hospital mortality rate was 12.5% (n=6). Patients with pulmonary nocardiosis had a

Table 3 - Different species of Nocardia isolated from various clinical specimen.

Clinical Specimen	*Number of samples*	*Nocardia asteroides*	*Nocardia nova*	*Nocardia otitidiscaviarum*	*Nocardia farcinica*	*Nocardia spp. unidentified*
Sputum	28	2	0	6	2	18
ET Aspirate	3	0	0	0	0	3
BAL	12	1	1	5	0	5
Pleural fluid	1	1	0	0	0	0
Brain abscess	1	0	0	0	0	1
Cutaneous abscess	2	0	0	0	0	2
Blood culture	1	0	0	0	0	1
Total n (%)	48	4 (8.3)	1 (2.1)	11 (22.9)	2 (4.2)	30 (62.5)

ET aspirate = Endotracheal aspirate; BAL = Bronchoalveolar lavage.

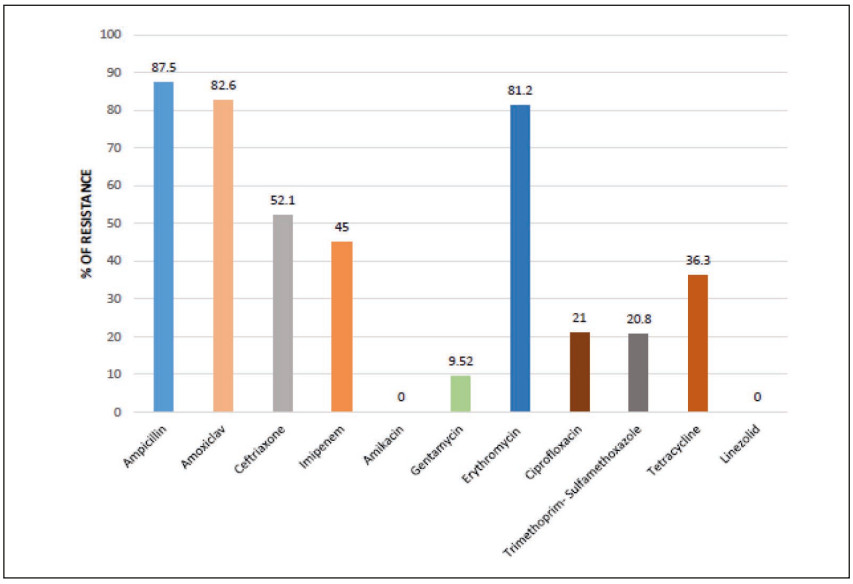

Figure 4 - Antibiotic resistance patterns.

Table 4 - Factors associated with outcome of nocardia infection.

Risk Factors		*Improved*	*Not improved*	*p-value*
Renal transplantation	Present	5	0	0.569
	Absent	33	10	
Corticosteroids	Present	19	3	0.307
	Absent	19	7	
HIV	Present	6	1	1.0
	Absent	32	9	
Chemotherapy	Present	3	0	1.0
	Absent	35	10	
Diabetes mellitus	Present	7	4	0.206
	Absent	31	6	
CKD	Present	3	0	1.0
	Absent	35	10	
COPD	Present	6	3	0.370
	Absent	32	7	
Bronchial asthma	Present	6	1	1.0
	Absent	32	9	
Active pulmonary TB	Present	6	1	1.000
	Absent	32	9	
Old pulmonary TB	Present	2	3	0.05*
	Absent	36	7	
Bronchiectasis	Present	4	0	0.566
	Absent	34	10	

HIV = Human immunodeficiency virus; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease.

higher mortality rate, and all deaths were related to either secondary bacterial infection in blood [*Enterococcus* spp. (n=1)] or ventilator associated pneumonia due to *Acinetobacter baumannii* (n=3), *Klebsiella* spp. (n=1) and *Pseudomonas aeruginosa* (n = 1). Four (8.3%) patients with pulmonary nocardiosis showed worsening during the hospital stay and were discharged at request due to financial constraints. The percentage of death was 33.3% and 5% respectively, among individuals with and without pulmonary tuberculosis. When the different variables were analysed with respect to clinical outcome, we observed that the patients with old pulmonary tuberculosis and later developing pulmonary nocardiosis showed significant association with poor outcome (p-value=0.05) as described in Table 4.

DISCUSSION

The incidence of nocardiosis seems to rise every year due to an increase in the number of immunocompromised patients, particularly those with altered cellular immunity, and also due to increased awareness [12]. However as previously mentioned, this infection can also occur in immunocompetent individuals [13]. We found a growing trend in cases of nocardiosis similar to other studies, possibly due to increased knowledge of the disease [12]. In our study, we also observed a sharp rise in cases in 2017 (16.7%) and 2019 (14.6%), when few parts of hospital were under construction. Considering the saprophytic distribution of *Nocardia* spp. in the soil, construction and other recreational activities in the hospital setting favours the spread of nocardial infection [14]. Males were affected more frequently than females in this study, similar to most of the published reports [15, 16]. The reason for this distribution could be related to hormonal effects on the virulence or growth of nocardia [17].

The most common underlying disease in the current study was chronic lung disease (52.1%). Among these patients, COPD (18.8%) was most commonly followed by bronchial asthma (14.6%). It has been reported that pulmonary co-morbidity, particularly COPD may be the only risk factor for nocardiosis [18]. Another important predisposing factor for the development of nocardiosis in our study was prolonged corticosteroid therapy (45.8%). In patients with chronic lung disease, especially COPD, impaired ciliary motility and epithelial damage lead to impaired local immune defence, and prolonged corticosteroid treatment may promote growth of *Nocardia* [19]. Furthermore, diabetes mellitus (22.9%), HIV infection (14.6%) and renal transplantation (10.4%) were found to be risk factors in our study. These observations were consistent with the results of other published studies [19, 20].

Clinically, diagnosing nocardial infection is difficult due to non-specific clinical manifestations that often resemble pulmonary tuberculosis. The most common symptoms in the study group were fever (87.5%), cough (79.2%) and breathlessness (52.1%) which was similar to the findings of previous studies [16, 19, 20]. The most frequent presentation was pulmonary disease (85.4%) in our series which is in unison with other studies [20, 21]. Some studies have observed that the radiological changes in pulmonary nocardiosis are varying, and may mimic a myriad of pulmonary diseases [22, 23]. In particular, consolidation (79.1%) was a common radiological finding in most of our patients and cavitation (4.1%) was found in very few. In a study by Chen et al., it was observed that most patients had single or multiple nodules (82.35%) and cavitation (76.47%) on thoracic computed tomography (CT) [22]. This discrepancy in the results may be because not all of our patients underwent CT thorax owing to financial constraints. Diagnosing pulmonary nocardiosis using radiological findings may be difficult since this approach is often associated with low specificity. However, clinical history in combination with radiological findings may provide important diagnostic clues. In this study, 14.6% of all evaluated patients had a disseminated disease. It is important to actively search for disseminated disease because it is directly related to the outcome and selection of definitive antibiotic therapy [13].

A definitive diagnosis of nocardiosis requires the isolation and identification of the organism from a clinical specimen. Even with non-invasive samples such as sputum, the yield is quite satisfactory, however invasive methods such as bronchoscopy may be required to obtain a quick diagnosis when patients do not produce sputum. In our study, 25% of the patients required bronchoscopy since they were unable to produce sputum. Nocardia usually takes three weeks for growth in routine aerobic cultures [24]. It is therefore important to

ask the microbiologist to incubate cultures for a longer period of time when a nocardia infection is suspected. Although *N. otitidiscaviarum* is rarely reported in pulmonary infections, accounting for only about 5% of all nocardia infections, it was frequently isolated from cultures in our study (22.9%) [25].

Trimethoprim-sulfamethoxazole (TMP-SMX), carbapenem, ceftriaxone, and amikacin, which are all generally recommended as initial treatment for nocardiosis, were the most frequently used antibiotics in our study [26, 27]. TMP-SMX is considered the standard first-line therapy for nocardiosis because most studies have shown that *Nocardia* is highly susceptible to this drug [16, 20]. Our study observed that 20.80% of *Nocardia* isolates were resistant to TMP-SMX which is quite high compared to previous study conducted by Lai et al. that revealed that 10% of isolates were resistant to TMP-SMX [28]. Uhde et al., in 2010 revealed high rate of resistance (42%) to TMP-SMX among 765 isolates of *Nocardia* [29]. In addition, we have found a high resistance rate to the most frequently used drug, ceftriaxone (52.10%), which is very high compared to some of the previous studies showing that all nocardia isolates were susceptible to ceftriaxone [26, 28]. Variation in resistance to different antimicrobials may be explained by differences in antibiotic usage practices in different healthcare settings. Therefore, taking into account the different antimicrobial resistance profile of different *Nocardia* spp., combination therapy with 2 or more active agents, including TMP-SMX, cephalosporin, amikacin, carbapenem and linezolid is recommended for patients with severe or disseminated disease [27].

In our study, we found that patients with old pulmonary tuberculosis showed a peculiar increase in mortality (p-value=0.05) compared to other commonly reported risk factors. This can be explained in terms of histopathological changes in the lungs caused by the progression of pulmonary tuberculosis. The fibrotic changes in lungs induced during the course of tuberculosis, advances co-infection or late infection of pulmonary nocardiosis, and increase exacerbation [30]. In the current series, no deaths were observed among patients with disseminated nocardiosis. This may be due to timely and appropriate management of infection with the existing knowledge of medical procedures and antibiotic combinations. On the contrary, mortality rate was higher among patients with pulmonary nocardiosis, with all deaths due to a subsequent secondary bacterial infection in the blood or ventilator associated pneumonia.

In summary, this study highlights that chronic lung disease, long-term steroid use and diabetes mellitus are the most common predisposing factors for nocardial infection. When there is lung involvement, clinicians usually suspect tuberculosis, particularly in immunocompromised individuals. Other aetiologies such as nocardiosis may need to be considered in patients with underlying structural lung disease or in those on chronic immunosuppressive therapy not responding to usual relevant therapy. Despite initial combination therapy mortality remains high, especially in those with secondary bacterial infection and requiring mechanical ventilation as seen in the present study. Therefore, early recognition and timely initiation of treatment of the disease are of particular importance for a better prognosis.

Conflict of interest

The authors declare no conflict of interest.

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