Original Article

Nocardiosis at an Organ Transplant Center in Saudi Arabia: 15 years' experience

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Abstract

Background: Nocardiosis is a rare infection that affects immunocompromised patients on immunosuppressive medications used for transplantation and cancer therapy. Such therapies are becoming more widely available in the Middle East region. Yet, reports on nocardiosis are scarce. **Materials and Methods:** This was a retrospective analysis of patients who were diagnosed with nocardiosis from 2004 to 2018 at a transplantation and cancer center. Nocardiosis were defined per the European Organization for Research and Treatment of Cancer criteria. **Results:** During the study period, 35 patients with nocardiosis (male: 68.5%) were identified. The most common underlying associated condition was transplantation 11 (31.4%), followed by malignancy 7 (20%), connective tissue disease and sarcoidosis 7 (20%), chronic lung disease 5 (14%), miscellaneous conditions 4 (11%), and one patient with human immunodeficiency virus. *Nocardia* was disseminated in 8 patients (22.9%) and isolated in 27 (77.1%); the latter included 13 patients (37.1%) with bronchial form, 11 (31.4%) with isolated visceral form, and 3 (8.6%) with cutaneous form. Pulmonary involvement occurred in 90% of the cases with cough, fever, and dyspnea being the most common symptoms. The main strain isolate was *Nocardia asteroides,* and the cure rate was 90%. Mortality related to nocardiosis occurred in 3 transplant patients (8.6%). **Conclusion:** Wider use of immunosuppressive therapy warrants vigilance to nocardiosis, which can present in a myriad of clinical forms. In our series, mortality was confined to the transplantation group, probably because of the relatively heavy immunosuppression. Nonetheless, prognosis is favorable if the infection is recognized and treated early.

Keywords: Bone marrow transplant, corticosteroids, immunocompromised host, immunosuppressive therapy, *Nocardia*, solid organ transplant

Introduction

Nocardiosis is a rare Gram-positive bacterial infection caused by aerobic actinomycetes in the genus *Nocardia*. Taxonomy of *Nocardia* has been revised and expanded based on the evolving molecular characterization and antimicrobial drug susceptibilities; *Nocardia asteroides* was, therefore, subsequently named as *N. asteroides* complex, which includes many subtypes.[1,2] The genus *Nocardia* is usually an "opportunistic pathogen" that classically causes infections in immunocompromised patients. Both solid organ transplant (SOT) and bone marrow transplant (BMT) are major risk factors for nocardiosis; graft rejection and immunosuppressive therapy are additional risk factors in those groups.[3-8] Other risk factors include malignancy, immune disease, diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), and human immunodeficiency virus (HIV) infection.[9-12]

In the Eastern Mediterranean Region (EMR) of the World Health Organization, an increasing incidence of cancer has been reported. Notably, the number of cases is projected to increase dramatically over the next 15 years. Similarly, there is an overall increased rate of hematopoietic stem cell transplantation in the EMR as well as solid organ transplantation and HIV infection rates.[13-15] This rise is likely to lead to more incidence of opportunistic infections including nocardiosis. Therefore, it is prudent to be vigilant about this serious infection, especially as it is potentially treatable if it is recognized early in those

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patients. Yet, there are only a few case series and case reports of *Nocardia* in EMR.[16-18] Hence, we performed a search in our microbiology database at our center, which is the main referral center for organ transplant and cancer therapy in the country, by reviewing all cases which were diagnosed with nocardiosis over a 15-year period (2004–2018). Our objective was to seek information regarding incidence, features, response to therapy, and risk factors associated with poor prognosis.

Materials and Methods

This was a retrospective study that was conducted at King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia, which is a large tertiary care referral hospital with a bed capacity of over 1200. A search was done for all cases in whom *Nocardia* was isolated by modified acid-fast bacillus stain and cultures of all clinical specimens in the microbiology laboratory database during the period (January 1, 2004–December 31, 2018). The patients' medical charts were reviewed, and the following information was obtained: sex, age, causes of immunocompromised status including organ transplantation, immunosuppressive therapy, malignancy, immune deficiency disorders, HIV infection, associated comorbidities, concomitant opportunistic infection and acute rejection for organ-transplanted patients, clinical presentations, laboratory results, microbiological cultures, radiological assessment, treatments, and outcome of the patients.

Definitions

In this study, we included all patients in whom *Nocardia* was isolated from clinical specimens. Pulmonary nocardiosis was classified to a proven or probable pulmonary *Nocardia* (PN) infection according to the European Organization for Research and Treatment of Cancer criteria for invasive aspergillosis;[19] patients had to fulfill one of the following conditions for study entry:

1. Proven PN: A positive culture from samples taken from a sterile primary site, for example, pleural effusion, blood, cerebrospinal fluid, tissue biopsy, or abscess puncture AND (i) radiological findings on chest X-ray or computerized tomography (CT) scan of the thorax compatible with pulmonary nocardiosis OR (ii) clinical signs and symptoms of a lower respiratory tract infection (cough, sputum, dyspnea, and fever >38.3°C).
2. Probable PN (one of the following): (i) a positive culture from sputum, tracheobronchial aspirate, or bronchoalveolar lavage AND (a) clinical signs and symptoms of a lower respiratory tract infection (cough, sputum, dyspnea, and fever >38.3°C) AND (b) radiological findings on chest X-ray or CT scan of the thorax consistent with pulmonary nocardiosis; (ii) microscopic proof of Gram-positive, branching, partially acid-fast filamentary bacteria in histological samples (identified as *Nocardia* spp.) AND (a) clinical signs and symptoms of a lower respiratory tract infection (cough, sputum, dyspnea, and fever >38.3°C) OR (b) radiological findings on chest X-ray or CT scan of the thorax consistent with pulmonary nocardiosis.

Patients were categorized to four clinical forms according to clinical presentations: (1) an isolated bronchial form defined by a proven or probable PN without radiological evidence of parenchymal lung or other organ involvement; (2) an isolated visceral form defined by a proven or probable PN with radiological evidence of involvement of one organ (in the case of the lung, evidence of lung parenchyma involvement [pneumonic form]); (3) a disseminated form defined as a positive culture from samples taken from a sterile primary site, for example, pleural effusion, blood, cerebrospinal fluid, tissue biopsy, or abscess puncture AND 2 or more organ localizations with detectable radiological evidence compatible with nocardiosis; and (4) an isolated cutaneous form.

Immunosuppressive medication was defined as chronic (>4 weeks) intake of steroids at a dosage of >10 mg prednisone or equivalent per day or the use of another immunosuppressive agent such as a calcineurin inhibitor (CNI), mycophenolate, cytostatic agent, mammalian target of rapamycin inhibitor, tumor necrosis factor-binding protein, or other biological therapies.

Ethics and statistics

This study was approved by the Institutional Review Board at our center. It was conducted in accordance with the protocol of its policies and guidelines and with the national and international ethical standards and policies of conducting research on human subjects such as Declaration of Helsinki.

For this retrospective study, all the statistical analysis of data was performed using the software package SAS version 9.3 (SAS Institute Inc., Cary, NC, USA). Descriptive statistics for the continuous variables were reported as mean ± standard deviation, and categorical variables were summarized as frequencies and percentages.

Results

A total of 35 cases of nocardiosis were identified during the period, with a range of follow-up of 12-156 months and a mean of 71 months. Nineteen patients were proven PN (54%), 13 patients were probable PN (37%), and 3 patients with cutaneous nocardiosis (9%).

Patient characteristics and underlying conditions

Table 1 summarizes the demographic and clinical characteristics of the patients, and Table 2 shows some of these features according to the clinical group. The age range of our studied patients was between 5 and 80 years (median: 58 years). The majority were males (68.5%).

At diagnosis, 20 patients (57.1%) have been receiving immunosuppressant medications for more than 3 months (steroids, CNI, mycophenolate mofetil or infliximab, antimetabolites, and a number of chemotherapeutic agents). Most were receiving combinations of these drugs (13 [37%] patients), while 7 patients (20%) only were on monotherapy. Three patients (8.5%) finished courses of chemotherapy shortly before the diagnosis of nocardiosis. Steroids were the most utilized immunosuppressive drug (15 of 20 patients) [Table 1].

A history of bone marrow or organ transplant was the most common associated, as outlined in Table 1. The mean interval between the

Table 1: Clinical and demographic characteristics

Characteristic	*n* (%)
Gender	
Males	24 (68.5)
Underlying condition	
Transplantation	11 (31.4)
BMT	6 (17.1)
Renal transplant	3 (8.5)
Liver transplant	1 (2.8)
Lung transplant	1 (2.8)
Malignancy	7 (20)
Squamous cell carcinoma	2 (5.7)
The larynx prostate adenocarcinoma	1 (2.8)
Hepatocellular carcinoma and large B-cell lymphoma	1 (2.8)
Non-Hodgkin lymphoma (S/P chemotherapy with no BMT)	2 (5.7)
Acute myeloid leukemia	1 (2.8)
Connective tissue disease and sarcoidosis	7 (20)
Sarcoidosis	2 (5.7)
Rheumatoid arthritis	1 (2.8)
Interleukin-12/interferon-gamma axis defect versus subtle T-cell dysfunction	1 (2.8)
Undifferentiated vasculitis	1 (2.8)
ILD secondary to Sjogren syndrome	1 (2.8)
Evans syndrome	1 (2.8)
Chronic lung disease	5 (14.2)
COPD	2 (5.7)
Bronchiectasis	1 (2.8)
ILD (idiopathic)	2 (5.7)
HIV	1 (2.8)
Other chronic medical disorders	4 (11.4)
Diabetes mellitus	3 (8.5)
Cardiovascular disorder	2 (5.7)
Madura foot	1 (2.8)
Morbid obesity	1 (2.8)
Stroke	1 (2.8)
Colon diverticulosis	1 (2.8)
Immunosuppressive treatment	
Monotherapy	7 (20)
Corticosteroids	6 (17.1)
Mycophenolate mofetil	1 (2.8)
Combination therapy	13 (37.1)
Steroids and CNI	6 (17.1)
Steroids and azathioprine	2 (5.7)
Steroids, methotrexate, and infliximab	1 (2.8)
Chemotherapy and CNI	1 (2.8)
Clinical forms	
Disseminated	8 (22.8)
Isolated	27 (77.1)
Isolated bronchial form	13 (37.1)
Isolated visceral (pneumonic) form	11 (31.41)
Isolated cutaneous form	3 (8.5)
Clinical presentation	
Cough	22 (62.8)
Fever	11 (31.4)
Dyspnea	8 (22.8)
Pain	3 (8.5)
Skin discharge	3 (8.5)
Abscess formation	1 (2.8)
Lymph node swelling	1 (2.8)
CNS	1 (2.8)
Outcome	
Cure	27 (77.1)
Death	8 (22.8)

BMT: Bone marrow transplant, CNI: Calcineurin inhibitor, CNS: Central nervous system, COPD: Chronic obstructive pulmonary disease, CT: Computerized tomography, DM: Diabetes mellitus, ILD: Interstitial lung disease, MRI: Magnetic resonance imaging, SCID: Severe combined immunodeficiency disease, S/P: Status post, TMP-SMX: Trimethoprim-sulfamethoxazole, HIV: Human immunodeficiency virus

transplantation and diagnosis of the infection was 9 months (range of 1.5–24 months); for the BMT group, the mean was 15 months, while for the SOT, it was 3.45 months. All organ transplant patients were receiving different combinations of under immunosuppressive agents except a child diagnosed with severe combined immunodeficiency disease RAG2 gene mutation. An episode of acute rejection was reported in 5 patients (14.2%) before the diagnosis of nocardiosis. Five patients (14.2%) were diagnosed with cytomegalovirus (CMV) with or without other opportunistic infections and were on treatments including acyclovir, antifungals, and doxycycline. Only one patient was receiving trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis at diagnosis.

A history of malignancy was observed in 7 (20%) patients [Tables 1 and 2]. No one at diagnosis was on TMP-SMX prophylaxis or on treatments for other infections.

Different disorders with derangement in the immune system including connective tissue disease and sarcoidosis were observed in 7 (20%) patients [Tables 1 and 2]. All were on single immunosuppressive therapy except one case with sarcoidosis. At diagnosis of nocardiosis, only one patient was on TMP-SMX prophylaxis.

Other associations included chronic lung disease, which was observed in 5 patients (14.2%). Of those, 3 patients had COPD; one of them had associated bronchiectasis, another had severe emphysema and was on chronic steroid therapy, and the last one had DM as well. The other 2 patients had interstitial lung disease, and they were on chronic steroid therapy.

There were three patients with DM but were otherwise immunocompetent. Two of them had cutaneous nocardiosis and responded to local medical treatment. The third patient suffered from stroke and sepsis and presented with pneumonia and pleural effusion. One immunocompetent patient had Madura foot and responded toTMP-SMX. Finally, HIV was diagnosed in one patient only (73 years old) on highly active antiretroviral therapy [Tables 1 and 2].

Clinical and laboratory characteristics

The isolated *Nocardia* form was found in 27 (77.1%) and

Table 2: Patients' clinical presentation characteristics according to the clinical form of nocardiosis

Parameter	General, *n* (%)	Form			
		Disseminated	Visceral	Bronchial	Cutaneous
		8 patients	11	13	3
Mean age, years	52.25	33	55	63	50
Underlying conditions, *n* (%)	35 (100)				
SOT	5 (14.2)	3	2	-	-
BMT	6 (17.1)	3	3	-	-
Malignancy	7 (20)	-	3	4	-
Immune disease	7 (20)	2	1	4	-
Chronic lung disease	5 (14.2)	-	-	5	-
Immunocompetent	4 (11.4)	-	1	-	3
HIV	1 (2.7)	-	1	-	-
Immunosuppressive drugs	20 (57.1)				
Steroids	15 (42.8)	4	5	6	-
Antimetabolites	3 (8.5)	-	1	2	-
Calcineurin inhibitors	7 (20)	4	3	-	-
Chemotherapy	4 (12.5)	1	2	1	-
Mycophenolate mofetil	1 (2.8)	1	-		-
Infliximab	1 (2.8)	-	-	1	-
No treatment	15 (42.8)	2	4	6	3
Symptoms					
Cough	22 (62.8)	3	10	8	-
Fever	11 (31.4)	5	6	-	-
Dyspnea	8 (22.8)	2	2	4	-
Pain	3 (8.5)	3	-	-	-
Skin discharge	3 (8.5)	-	-	-	3
Abscess formation	1 (2.8)	1	-	-	-
Lymph node swelling	1 (2.8)	1	-	-	-
CNS manifestation	1 (2.8)	1	-	-	-
Radiological characteristics					
New pulmonary infiltrates	19 (54.2)	8	11	0	0
No new pulmonary infiltrates	16 (45.7)	-	-	13	3
Outcome, *n* (%)					
Death due to nocardiosis	3 (8.5)	1	2	-	-
Death due to primary disease	5 (14.2)	-	3	2	-
Cure without sequela	27 (77.1)	7	6	11	3

SOT: Solid organ transplant, BMT: Bone marrow transplant, HIV: Human immunodeficiency virus, TMP-SMX: Trimethoprim-sulfamethoxazole

included 13 patients (37.1%) with the bronchial form, 11 patients (31.4%) with the isolated visceral form (in our series, all involved lung only [pneumonic]), and 3 patients (8.6%) with the cutaneous form. The disseminated form was diagnosed in 8 (22.9%) patients. The main symptoms were cough (60%), fever (31.4%), dyspnea (22.8%), and others, as shown in Tables 1 and 2. Laboratory tests showed leukocytosis in 22.8% of the patients and lymphopenia in 25.7% of the patients.

Radiological characteristics

Radiological assessment by chest radiography and CT was done for all patients with the exception of one immunocompetent patient with cutaneous lesion [Tables 2 and 3]. New radiological findings were recorded in 19 patients (54.2%); all patients with organ transplant (11) and 3 patients with malignancy had new radiological findings. None of the patients with bronchial form and chronic lung diseases had any new radiological findings.

Microbiological characteristics

Nocardia strains were isolated from the sputum of 28 patients (80%); isolated species and the type of clinical sample that yielded the growth are shown in Table 4. Six cases of *Nocardia asteroids* were further speciated by biochemical testing, and *Nocardia farcinica* was identified in 4 and *Nocardia cyriacigeorgica* in 2. Nucleic acid amplification assays were not performed.

Treatment and outcome

There were 8 documented deaths; 5 were due to progression of the primary disease and 3 were related directly to nocardiosis. All the nocardiosis-related mortalities occurred in the organ transplant patients with isolated pneumonic form [Tables 1 and 2]. Of the 27 patients (77.1%) with isolated forms, 20 (57.1%) recovered completely after antibiotic therapy [details are shown in Table 4]. Among 8 (22.8%) patients with disseminated form, 4 were treated with TMP-SMX only and all recovered. The

Table 3: Radiological characteristics*

Radiological finding	*n* (%)
New radiological infiltrates	19 (56)
No new radiological infiltrates (bronchial form)	13 (38)
Normal (cutaneous form)	2 (5.9)
Lymph nodes	19 (560)
Mediastinal	4 (12)
Hilar	1 (2.9)
Parenchymal	
Normal	3 (8.8)
Abnormal	
Reticulation	6 (17.6)
Consolidation	11 (32.3)
Ground glass	6 (17.6)
Nodule	5 (14.7)
Cavity	3 (8.8)
Mass	1 (2.9)
Pleural effusion	6 (17.6)

*By chest radiography and computerized tomography of the chest (no. 34 patients)

Table 4: Microbiological characteristics and antibiotics

Parameter	*n* (%)
Source of the diagnostic sample	
Sputum	28 (80)
Blood culture	2 (5.7)
Tissue culture	2 (5.7)
Skin swabs	3 (8.5)
Isolated species	
Nocardia asteroides	28 (80)
Nocardia brasiliensis	5 (14.2)
Nocardia otitidiscaviarum	2 (5.7)
Treatment	
TMP-SMX alone	17 (48.5)
TMP-SMX with other antibiotics	7 (20)
TMP-SMX and carbapenem	2 (5.7)
TMP-SMX, imipenem, and amikacin	3 (8.5)
TMP-SMX, amoxicillin/clavulanic acid, and levofloxacin	1 (2.8)
TMP-SMX and itraconazole	1 (2.8)
Other combinations	11 (31.4)

TMP-SMX: Trimethoprim-sulfamethoxazole

other 4 were treated with combination therapy [Table 4]; 3 responded and one died due to progressive nocardiosis. There were no relapses in either group during the follow-up period.

Discussion

Nocardiosis is a rare disease that occurs primarily in immunocompromised patients, usually as a consequence of drugs, organ transplant, malignancy, immune disease, or infection. Immunosuppressive drugs are one of the major risk factors of nocardial infection, especially corticosteroids, which are used in the management of a wide range of medical conditions.[20-22] In our study, most of the patients (57.1%) were on single or multiple immunosuppressive medications for over 3 months; corticosteroid therapy is the most common one. In addition, in our cohort, nocardiosis occurred mostly in the older age group, a finding that was noted previously,[23] probably reflecting the declining immunity and multiple comorbidities. Finally, there was only one patient with HIV, reflecting the low prevalence in the region.

The underlying medical conditions determine the bacteriological spread and hence clinical picture of nocardiosis.[11,24] In our cohort, organ transplant was the main underlying medical condition in nearly a third of the patients, and the proportion in previous studies ranged between 18.1%–44.1%.[25,26] Such variation is probably explained by different referral patterns and patient populations. This high prevalence of nocardiosis in posttransplant patients is probably related to severe degree of immunosuppression related to therapy.[27] Nearly half of our patients had episodes of acute rejection before the diagnosis of nocardiosis, another half had opportunistic infections, and all had CMV infections, and all nocardiosis-related deaths (3 patients) occurred in this group of patients.

All four different clinical forms were seen in our patients: an isolated pneumonic form, an isolated bronchial form, a disseminated form, and an isolated cutaneous form.[25] Pulmonary involvement either as an isolated or disseminated form is very common in nocardiosis,[22] and indeed, this was observed in over 90% of our patients. An underlying chronic lung disease was observed in all patients with the bronchial form but not in the patients with the isolated pneumonic form. In terms of symptoms, cough has been reported to be the most common among the respiratory symptoms,[28] which was again noted in our series. Fever was observed in the isolated visceral pneumonic form, while the bronchial form was characterized by dyspnea. The disseminated form was observed in 22.8% of the patients, higher than figures previously reported in the literature (6%–13.5%).[26,29] This might be attributed to the extensive use of the available radiological resources at our center that included full-body CT scanning and magnetic resonance imaging. In addition, many patients presented with multiple symptoms which may have alerted the treating physician to possible dissemination of the disease. The radiological findings in our patients were variable and nonspecific, with consolidation being the most common feature, which was reported in previous series,[17,19] with the exception of a higher number of patients with mediastinal lymphadenopathy. The isolated cutaneous form is usually observed in elderly patients with comorbidities.[20] Three of our patients (two with the isolated cutaneous form and one with the bronchial form) only had DM, and one had Madura foot without any other comorbid medical condition or immunosuppressive therapy.

Similar to previous studies,[30] the main strain isolate in our study was *N. asteroides*. All our patients were treated by TMP-SMX either alone or with other drugs for an average of 5.4 months, with a curative rate of 90% (after excluding patients whose death was attributed to progression of primary disease). This is consistent with other studies that showed a similar success rate with a comparable treatment duration.[27] The *Nocardia*-related

mortality rate in our study was 8.6% (3/35) which is lower than other reported studies[26] and may be related to early detection and treatment of the infection. There were five other mortalities due to the progression of the primary disease.

Limitations are bound to occur in this study because of its retrospective nature and the small number of patients. However, this was the case in nearly all previously reported series which had a similar number of patients or less basically because of the rarity of nocardiosis. Nonetheless, we believe that it is important to report this infection to emphasize vigilance, and surveillance, particularly among vulnerable groups.

Conclusion

Nocardiosis is a rare opportunistic infection in immunocompromised patients, including organ transplant recipients. Of note, all *Nocardia*-related mortalities occurred in this group of patients. A variety of clinical forms and the associated risk factors were observed in our study, with the isolated bronchial form being the most common. Prognosis and response to therapy is excellent if the infection is diagnosed and treated early. Because of the rarity of nocardiosis, multicenter collaborative prospective research on the epidemiologic, diagnostic, and therapeutic aspects of nocardiosis is warranted.

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Conflicts of interest

There are no conflicts of interest.

References

1. Brown-Elliott BA, Brown JM, Conville PS, Wallace RJ Jr., Clinical and laboratory features of the *Nocardia* spp. based on current molecular taxonomy. Clin Microbiol Rev 2006;19:259-82.
2. Fatahi-Bafghi M. Nocardiosis from 1888 to 2017. Microb Pathog 2018;114:369-84.
3. van Burik JA, Hackman RC, Nadeem SQ, Hiemenz JW, White MH, Flowers ME, *et al*. Nocardiosis after bone marrow transplantation: A retrospective study. Clin Infect Dis 1997;24:1154-60.
4. Forbes GM, Harvey FA, Philpott-Howard JN, O'Grady JG, Jensen RD, Sahathevan M, *et al*. Nocardiosis in liver transplantation: Variation in presentation, diagnosis and therapy. J Infect 1990;20:11-9.
5. Stack WA, Richardson PD, Logan RP, Mahida YR, Hawkey CJ. *Nocardia asteroides* lung abscess in acute ulcerative colitis treated with cyclosporine. Am J Gastroenterol 2001;96:2255-6.
6. Tada Y, Fukuoka M, Mitamura M, Koarada S, Suematsu R, Inoue H, *et al*. Nocardiosis in adult-onset Still's disease and vasculitis syndrome. Am J Med Sci 2008;336:77-80.
7. Arduino RC, Johnson PC, Miranda AG. Nocardiosis in renal transplant recipients undergoing immunosuppression with cyclosporine. Clin Infect Dis 1993;16:505-12.
8. Roberts SA, Franklin JC, Mijch A, Spelman D. *Nocardia* infection in heart-lung transplant recipients at Alfred Hospital, Melbourne, Australia, 1989-1998. Clin Infect Dis 2000;31:968-72.
9. Beaman BL, Beaman L. *Nocardia* species: Host-parasite relationships. Clin Microbiol Rev 1994;7:213-64.
10. Abreu C, Rocha-Pereira N, Sarmento A, Magro F. *Nocardia* infections among immunomodulated inflammatory bowel disease patients: A review. World J Gastroenterol 2015;21:6491-8.
11. Lederman ER, Crum NF. A case series and focused review of nocardiosis: Clinical and microbiologic aspects. Medicine (Baltimore) 2004;83:300-13.
12. Pintado V, Gómez-Mampaso E, Cobo J, Quereda C, Meseguer MA, Fortún J, *et al*. *Nocardia*l infection in patients infected with the human immunodeficiency virus. Clin Microbiol Infect 2003;9:716-20.
13. International Agency for Research on Cancer [IARC] and World Health Organization. GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012. Geneva: World Health Organization; 2012.
14. Mohamed SY, Fadhil I, Hamladji RM, Hamidieh AA, Fahmy O, Ladeb S, *et al*. Hematopoietic stem cell transplantation in the Eastern Mediterranean Region (EMRO) 2008-2009: Report on behalf of the Eastern Mediterranean Bone Marrow Transplantation (EMBMT) Group. Hematol Oncol Stem Cell Ther 2011;4:81-93.
15. UNAIDS Data. Available from: https://www.unaids.org/sites/default/files/media_asset/2019-UNAIDS-data_en.pdf. (Accesed 12 April 2020)
16. Hakawi AM, Al Rabiah FA. Clinical pattern of nocardiosis in Saudi Arabia: A case series. East Mediterr Health J 2008;14:966-71.
17. Al-Jahdali H, Baharoon S, Alothman S, Memish Z, Waness A. Nocardiosis in a tertiary care hospital in Saudi Arabia. J Glob Infect Dis 2011;3:128-32.
18. Alavi Darazam I, Shamaei M, Mobarhan M, Ghasemi S, Tabarsi P, Motavasseli M, *et al*. Nocardiosis: Risk factors, clinical characteristics and outcome. Iran Red Crescent Med J 2013;15:436-9.
19. Ott SR, Meier N, Kolditz M, Bauer TT, Rohde G, Presterl E, *et al*. Pulmonary nocardiosis in Western Europe-Clinical evaluation of 43 patients and population-based estimates of hospitalization rates. Int J Infect Dis 2019;81:140-8.
20. Yang M, Xu M, Wei W, Gao H, Zhang X, Zhao H, *et al*. Clinical findings of 40 patients with nocardiosis: A retrospective analysis in a tertiary hospital. Exp Ther Med 2014;8:25-30.
21. Cattaneo C, Antoniazzi F, Caira M, Castagnola C, Delia M, Tumbarello M, *et al*. *Nocardia* spp infections among hematological patients: Results of a retrospective multicenter study. Int J Infect Dis 2013;17:e610-4.
22. Hernandez-Hernandez F, Lopez-Martinez R, Mendez-Tovar LJ, Manzano-Gayosso P. *Nocardia brasiliensis*: *In vitro* and *in vivo* growth response to steroid sex hormones. Mycopathologia 1995;132:79-85.
23. Vasson MP, Farges MC, Goncalves-Mendes N, Talvas J, Ribalta J, Winklhofer-Roob B, *et al*. Does aging affect the immune status? A comparative analysis in 300 healthy volunteers from France, Austria and Spain. Immun Ageing 2013;10:38.
24. Sorrel T, Mitchell DH, Iredell JR, Chen SC. *Nocardia* species. In: Mandell GL, Bennett JE, Dolin R, editors. Principles and Practice of Infectious Diseases. 7th ed.. Philadelphia: Churchill Livingstone/Elsevier; 2010. p. 3199-207.
25. Haussaire D, Fournier PE, Djiguiba K, Moal V, Legris T, Purgus R, *et al*. Nocardiosis in the south of France over a 10-years period, 2004-2014. Int J Infect Dis 2017;57:13-20.
26. Minero MV, Marín M, Cercenado E, Rabadán PM, Bouza E, Muñoz P. Nocardiosis at the turn of the century. Medicine (Baltimore) 2009;88:250-61.
27. Peleg AY, Husain S, Qureshi ZA, Silveira FP, Sarumi M, Shutt KA, *et al*. Risk factors, clinical characteristics, and outcome of *Nocardia* infection in organ transplant recipients: A matched case-control study. Clin Infect Dis 2007;44:1307-14.
28. Hui CH, Au VW, Rowland K, Slavotinek JP, Gordon DL. Pulmonary nocardiosis re-visited: Experience of 35 patients at diagnosis. Respir Med 2003;97:709-17.
29. Liu WL, Lai CC, Ko WC, Chen YH, Tang HJ, Huang YL, *et al*. Clinical and microbiological characteristics of infections caused by various *Nocardia* species in Taiwan: A multicenter study from 1998 to 2010. Eur J Clin Microbiol Infect Dis 2011;30:1341-7.
30. Bell M, McNeil MM, Michael, Brown JM. *Nocardia* species [nocardiosis]–infectious disease and antimicrobial agents. Epidemiology and Surveillance Division National Immunization Program. Centers for Disease Control and Prevention, Atlanta; 2017. Available from: http://www.antimicrobe.org/b117.asp. (Accessed 12 April 2020).