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Impact of immune status on the clinical characteristics, treatment outcomes and mortality of pulmonary nocardiosis: a retrospective analysis in a tertiary care hospital from a low to middle-income country

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Abstract

Nocardiosis is an opportunistic infection that primarily targets the immunosuppressed. We investigate the differences in demographics and characteristics between immunosuppressed and immunocompetent patients with nocardiosis in a tertiary care hospital in Pakistan. Retrospective records were reviewed for patients diagnosed with pulmonary nocardiosis between 2010 and 2020. Immunosuppressed individuals were identified as those with autoimmune diseases, hematologic diseases and malignancies, HIV, immunosuppressant therapy, *etc*. Data collected included basic demographics, comorbid conditions, medication history, clinical presentation, radiological and microbiological data, and nocardiosis outcomes and complications. A total of 66 patients with nocardiosis were included in this study out of which 48 were immunosuppressed while 18 were immunocompetent. Both groups were compared for a number of variables including patient characteristics, underlying conditions, radiological findings, treatment regimen and outcomes. Immunosuppressed individuals were younger, and had higher rates of diabetes, chronic renal disease, chronic liver disease, higher platelet counts, surgical intervention, and longer hospital stays. Fever, dyspnea, and sputum production were the most common presentations. *Nocardia asteroides* was found to be the most common species of *Nocardia* overall. Nocardiosis presents differently in patients with immunosuppressed and immunocompetent patients consistent with previous studies. Nocardiosis should be considered in any patient presenting with treatment-resistant pulmonary or neurological symptoms

Key words: Immune status, pulmonary nocardiosis, Pakistan

Introduction

Nocardiosis is an opportunistic infection caused by the actinomycete, *Nocardia* causing invasive presentations in the immunosuppressed (1,2) .Pulmonary infection is most common, with possible dissemination to other sites (3). Deficiencies in cell-mediated immunity pose a particular risk for nocardiosis (4). Two studies have compared radiological, microbiological, and clinical characteristics of nocardiosis stratified by immunocompetency (5,6).

Differences in radiological features of nocardiosis based on immunocompetency may help in diagnosis. Similarly, variations in antibiotic efficacy based on immunocompetency may improve regimen development (7,8). This study reviews radiological, microbiological, and clinical characteristics of nocardiosis cases presenting to a tertiary-care hospital in Pakistan over 18 years.

Material and Methods

Study setting and population

This retrospective observational study was conducted at The Aga Khan University Hospital, a large 560-bed tertiary care center located in Karachi, Pakistan. This study includes all adult patients ((>18 years old) with culture-proven pulmonary nocardiosis who underwent clinical, radiological, microbiological and laboratory investigations in both outpatient and inpatient settings between January 1, 2010, and July 31, 2020.

Data collection

The study was approved by AKU ethical review committee (ERC # 2019-0801-1195). Patient charts were reviewed for all identified individuals diagnosed with pulmonary nocardiosis using the International Classification of Disease, Ninth Revision codes (ICD-9 1173). The pertinent information was collected on a predesigned proforma.

The proforma consisted of a structured questionnaire on the demographics, co-morbid conditions, clinical presentation, microbial profile, laboratory findings, treatment, complications, and long-term outcomes. Care was taken to omit any patient identifiers from the extracted information.

Study definitions

Immunosuppressed patients (ISP)

Immunosuppression is defined as a lack of white blood cell response to foreign or abnormal antigens which could be primary or secondary. Primary immunosuppression causes include hereditary conditions and are usually present at birth and secondary immunosuppression can be caused by viruses, malignancies, medications or autoimmune conditions (9-11). Immunosuppressed patients were defined as those with autoimmune illnesses, hematologic disease, active solid organ or hematologic malignancies, HIV infection, solid organ transplantation and any condition requiring long-term immunosuppressive therapy. Immunosuppressive therapy was defined as the recent use of systemic corticosteroids, chemotherapy, or other T-cell immunosuppressants within three months of hospital or clinic presentation (12).

Conditions such as chronic obstructive pulmonary disease (COPD), diabetes mellitus, chronic kidney disease, and chronic liver disease, past pulmonary tuberculosis which do not require immunosuppressive therapy, were regarded as immunocompetent (ICP) (13).

Statistical analysis

Characteristics and outcomes of immunocompetent and immunosuppressed patients were compared. Categorical variables were compared using the Chi-Square with Yate's Continuity Correction or Fisher's exact test. Mann-Whitney U test was conducted for all continuous variables with non-parametric distributions, assessed using the Shapiro-Wilk test. Statistical tests for differences between the two subgroups were forgone on account of the small sample size. All statistical analyses were conducted independently by two authors using the open-source software R version 4.1.2 (The R Project for Statistical Computing, packages: *dplyr, naniar*) and SPSS version 22 (IBM).

Results

Demographics and clinical features

Upon retrospective review, 66 patients with pulmonary nocardiosis were identified; 48 (73%) were identified as immunosuppressed, while the remaining 18 (27%) satisfied the study's definition of immunocompetent. Their demographics, comorbid conditions, immunotherapy profile, and disease presentation characteristics are described stratified by immune status in Tables 1 and 2.

The mean age of the ISP group was found to be lower than that of ICP (54.52 and 62.94 years, respectively). Rates of comorbid type two diabetes mellitus (33% in ISP, 28% in ICP) and hypertension (52% in ISP, 61% in ICP) were comparable between the two populations. ISP had higher rates of chronic renal (25% in ISP, 6% in ICP) and liver (8% in ISP, 6% in ICP) disease. Rates of past pulmonary TB infections were also higher in the ICP group (10% in ISP, 39% in ICP);. 6 (12%) of the ISP had solid organ malignancy, 2(4%) had undergone solid organ transplantation, 23 (48%) had underlying autoimmune disease, and 9 (19%) had underlying hematological disease; 40 (83%) of these individuals were under corticosteroid therapy, 5 (10%) were undergoing chemotherapy, and 16 (33%) were under some other form of immunosuppressant therapy. The most common presenting complaints among the entire study sample were fever (67%), dyspnea (65%), and sputum production (58%), and remained so after stratification according to immune status. Weight loss as a presentation was observed at higher rates in ICP individuals (12% in ISP vs. 56% in ICP). The presence of neurological symptoms such as headache (6% in ISP), drowsiness (10% in ISP), seizures (6% in ISP), and vertigo (2% in ISP) were solely present in immunosuppressed individuals. Extrapulmonary involvement was found in 8 patients in this study, 5 in the immunosuppressed, and 3 in the immunocompetent group. The site of involvement for all these patients was the CNS. The most common method of diagnosing pulmonary nocardiosis in our patient population was through sputum analysis in both sample subsets (52% in ISP, 11% in ICP), followed by bronchoalveolar lavage (21% in ISP, 17% in ICP) (Table 3). *N. asteroides* was found to be the most common species of *Nocardia* in our population, causing disease in 25(52%) of ISP, and 12(67%) of ICP. 14 individuals in our study presented with concomitant bacterial infection. 12 individuals presented with concomitant fungal infections, and three ISP presented with concomitant tuberculosis (Table 3).

Radiological and laboratory investigations

Radiological findings have been represented in Table 4. Higher mean platelet counts were reported in ISP (340.4) than in ICP (262.8). Other collected parameters including hemoglobin, leukocyte count, and c-reactive protein were found to be comparable.

Treatment regimen

85% of ISP and 78% of ICP in our study were treated using trimethoprim-sulfamethoxazole (TMP-SMX). Additionally, carbapenem was used in 38% of ISP and 28% of ICP and amikacin was used in 17% of ISP and 11% of ICP. Less common agents are reported in Table 5.

Resistance patterns of drugs

Of the *N. asteroides* samples tested for drug sensitivities, 37(100%) were sensitive to amikacin, 32(86.5) to trimethoprim-sulfamethoxazole, 22(59.5%) to minocycline (14(37.8%) intermediate sensitivity samples), 17(45.9%) to ceftriaxone (1(1.5%) intermediate sensitivity sample), 4(10.8%) to ciprofloxacin (6(16.2%) intermediate sensitivity samples), 9(24.3) to amoxicillin-clavulanic acid (3(8.1%) intermediate sensitivity samples), 17(45.9%) to linezolid, and 10(27.0%) to Imipenem (4(10.8%) intermediate sensitivity samples). Of the non-asteroides samples tested for drug sensitivities, 26(100%) were sensitive to amikacin, 27(93.1%) to trimethoprim-sulfamethoxazole, 17(58.6%) to minocycline (9(31.0% intermediate sensitivity samples), 19(65.5%) to ceftriaxone, 3(10.3%) to ciprofloxacin, 6(20.7%) to amoxicillin-clavulanic acid (1(3.4% intermediate sensitivity sample), 16(55.2%) to linezolid, and 7(24.1%) to imipenem (5(17.2%) intermediate sensitivity samples).

Outcomes

17% of ISP required surgical intervention for their disease, comparable to 11% of ICP (p=0.715). Half of all individuals experienced some sort of disease complications such as respiratory failure, required mechanical ventilation, septicemia, abscess formation, renal dysfunction, liver dysfunction, pneumothorax, or empyema. The mean length of stay for ISP was 10.7 days compared to 7.6 days for ICP(p=0.08). Symptom duration was similarly longer in ISP (2.6 days) vs ICP (2 days) groups. As represented in Table 5, 16(33%) of ISP and six (33%) of ICP expired because of their disease and concurrent medical issues. Disease in all ages was most likely to result in mortality if individuals were immunosuppressed. 13(35%) of ISP males and three (30%) of ICP males expired, in comparison to four (36%) ISP females, and three (38%) ICP females. ISP patients were more likely to expire if they had concomitant bacterial or fungal infections compared to their ICP counterparts. One ISP patient out of Two with solid transplant history and one patient out of

two with interstitial lung disease (ILD) also expired. Three individuals in both ISP and ICP with chronic obstructive pulmonary disease (COPD) also expired.

Discussion

This study included 66 patients admitted to our tertiary care hospital over a period of 17 years with Nocardiosis. After analysis of patient's details, laboratory and radiological investigations and course of the disease it is quite evident that most of the variables encompassing demographics, clinical presentation, laboratory values, radiological evidence, treatment regimen and outcomes were similar in the immunosuppressed and the immunocompetent groups.

In our study, the distribution of male patients was slightly higher in the immunosuppressed patients which is also true in studies published by Steinbrink *et al*. and Kim *et al*. (5,6). Overall males have a higher chance of acquiring *Nocardia* infection as reported in the literature in several studies. (5,6,14,15) The mean age of patients in the immunocompetent group is higher than immunosuppressed group in our study, similarly reflected in previous studies (5,6).

In the analysis of underlying conditions of patients with nocardiosis, hypertension was the most common underlying condition overall in our study while in previous studies type two diabetes mellitus was the most common underlying condition excluding any conditions defining immunosuppression. (5,16) Moreover, our study showed high usage of corticosteroids in patients with nocardiosis with past corticosteroid therapy identified as a major risk factor for the development of nocardiosis (16,17). This reinforces current guidelines for individuals undergoing corticosteroids that suggest trimethoprim-sulfamethoxazole therapy to empirically reduce the risk of nocardiosis (14).

Our study showed that most underlying conditions, except for the ones that defined immunosuppression, were similar in both groups with chronic renal failure as the only underlying condition being higher in patients who are immunocompetent. Moreover, the patients who immunocompetent individuals with a past history of pulmonary tuberculosis have a higher risk of developing nocardiosis compared to their immunosuppressed counterparts. The authors find this a paradoxical relationship conceptually and suggest further validation because of the small sample size of patients with a history of pulmonary TB. Steinbrink *et al*. and Kim *et al*. found type two diabetes mellitus rates to be significantly higher in immunosuppressed individuals, whereas the

immunosuppressed showed higher rates of individuals meeting the criteria of alcohol abuse in the former study and chronic lung disease in the latter (5,6).

The most common presenting symptoms of nocardiosis reported in literature have been fever and cough (5,14,18,20). The most frequent symptoms of disease in our study were fever followed by shortness of breath. In the immunocompetent group the number of patients presenting with weight loss was higher compared to the immunosuppressed group.

The most common source used for culture was sputum samples, consistent with the most common source used for diagnosis in previously reported studies (14,20). Concomitant infections should not be disregarded in patients with nocardiosis. Our study revealed fungal and bacterial concomitant infections in about one fifth of the cases. Similar rates of concomitant infections have been reported in literature (5).

In patients who underwent CT scan the most common findings were bilateral infiltrates and multi-lobar infiltrates. Other findings reported on CT were unilateral infiltrates, pleural effusion, pleural mass, cavitations, consolidation, and nodules. Payam et al. in 2015 studied CT features of 25 patients presenting with nocardiosis and report multiple pulmonary nodules (96%) as the most common finding followed by consolidation (76%) and cavitations (52.2%) (21). Blackmon *et al.* similarly reported consolidation (64.2%), nodules (56.6%) and cavitations (39.6%) on CT as the most common presenting findings (22).

In addition, their study found that discrete nodules were associated with immunosuppression (22). Likewise, Kim e*t al*. and Steinbrink *et al*. reported cavitation as a finding on CT scan being significantly higher in patients with immunosuppression (5,6).

Similar rates of CNS dissemination were found between immunocompetent and immunosuppressed groups, as reflected by the results reported by a previous study (5). Hence, the authors suggest that choice of MRI or CT to look for CNS involvement should not be influenced by the patient's immune status until further review.

About 15% of patients required surgical intervention in our population. In a retrospective study conducted in France, surgical intervention was indicated in 38.2% of the study's sample (19). Disease complications were observed in about half of the patients in our study with similar rates (Table 4). Conversely, Steinbrink *et al.* reported higher rates of disseminated infection in the immunosuppressed patients (6).

In our study, the mean duration of hospital stay and the mean duration of symptoms was higher in the immunosuppressed group. Longer duration of hospitalization has been associated with immunosuppression in a previous study (5).

N. asteroides was the most common form of *Nocardia* identified in our study which was conducted in Pakistan. Two studies in South Korea and France have reported *N. cyriacigeorgica* and *N. farcinica* as their most common forms of *Nocardia*, indicating that there might be geographical differences in causative species (5,19).

The mean values of laboratory parameters including C-reactive protein, hemoglobin and leukocyte levels were similar in both groups with mean platelet count being slightly lower in the immunocompetent group. Kim et al. also report similar mean values of laboratory parameters in the comparison groups (5).

In our study, trimethoprim-sulfamethoxazole followed by carbapenems were the most common treatment options. In a study published in Spain, the use of trimethoprim-sulfamethoxazole was at similar rates to the use in our study population and it remains the first choice and the most used therapy worldwide for nocardiosis (14,16).

In our study, both groups had similar mortality and there was little difference amongst the groups on the basis of gender or age. Respiratory failure was the most common cause of mortality in our study population. Our reported mortality rate is 33% which is quite similar to what has been reported by Zia *et al*. (23). Some studies report lower mortality rates while some report even higher mortality rates (5,18).

Limitations

This study is a single-center retrospective study which may not be reflective of a larger geographical area than served by the hospital. Some missing data creates further limitations in this study, reducing the sample size. Overall, this study is the first of its kind conducted in Pakistan in one of the country's leading tertiary care hospitals which frequently receives critically ill cases from all over the country and abroad, beyond its catchment area. Any differences highlighted in the text may not be generalizable to the general population due to the limited size, because of which tests of statistically significant differences were not employed in this study. This study serves as a good reference study for the development of future guidelines concerning pulmonary nocardiosis in Pakistan.

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Table 1. Characteristics and underlying conditions.

	Immunosuppressed (n=48)	**Immunocompetent (n=18)**	**Total (n=66)**
Characteristic			
Age, years, mean	54.5	62.9	56.8
Male, n, (%)	35(73%)	9(53%)	44(68%)
Underlying conditions, n, (%)			
No underlying disease			
Diabetes	16(33%)	5(28%)	21(32%)
Hypertension	25(52%)	11(61%)	36(55%)
Chronic renal failure	12(25%)	1(6%)	13(20%)
Chronic liver disease	4(8%)	1(6%)	5(8%)
Past pulmonary tuberculosis	5(10%)	7(39%)	12(18%)
Chronic lung disease	15(31%)	10(59%)	25(39%)

Table 2. Presentation of disease.

	Immunosuppressed (n=48)	Immunocompetent (n=18)	Total (n=66)
Presentation of disease, n, (%)			
Cough	19(40%)	6(33%)	25(38%)
Sputum	25(52%)	13(72%)	38(58%)
Hemoptysis	9(19%)	4(22%)	13(20%)
Dyspnea	29(60%)	14(78%)	44(65%)
Chest pain	5(10%)	3(17%)	8(12%)
Fever	34(71%)	10(56%)	44(67%)
Weight loss	6(12%)	10(56%)	16(24%)
Fatigue	8(17%)	5(28%)	13(20%)
Loss of appetite	7(15%)	5(28%)	12(18%)
Headache	3(6%)	0	3(5%)
Cutaneous ulcer	1(2%)	0	1(2%)
Drowsiness	5(10%)	0	5(8%)
Seizures	3(6%)	0	3(5%)
Vertigo	1(2%)	0	1(2%)
Limb weakness	1(2%)	0	1(2%)

Table 3. Mode of diagnosis and concomitant infection.

	Immunosuppressed (n=48)	Immunocompetent (n=18)	Total (n=66)
Mode of diagnosis, n, (%)			
Sputum	25(52%)	11(61%)	36(55%)
Tracheal aspiration	5(10%)	2(11%)	7(11%)
Bronchoalveolar lavage	10(21%)	3(17%)	10(20%)
Pleural fluid	2(4%)	0	2(3%)
Pleural tissue	4(8%)	2(11%)	6(9%)
Pus culture	1(2%)	0	1(2%)
Concomitant infection, n, (%)			
Bacterial	10(21%)	4(22%)	14(21%)
Fungal	10(21%)	2(11%)	12(18%)
Tuberculosis	3(6%)	0	3(5%)

Table 4. Radiological findings.

	Immunosuppressed (n=48)	Immunocompetent (n=18)	Total (n=66)
Radiological plain radiograph findings, n, (%)			
Unilateral	14(29%)	7(39%)	21(32%)
Bilateral	30(62%)	9(50%)	39(59%)
Multilobar	28(58%)	11(61%)	39(59%)
Nodules	19(40%)	2(11%)	21(32%)
Pleural effusion	8(17%)	3(17%)	11(17%)
Consolidation	14(29%)	7(39%)	21(32%)
Cavitation	4(8%)	1(6%)	5(8%)
Radiological computed tomography findings, n, (%)			
Ct performed	28	11	39
Unilateral	4 /28(14%)	3/11 (27%)	7/39 (18%)
Bilateral	24/28 (86%)	8/11 (73%)	3239 (82%)
Multilobar	24/28 (86%)	9/11 (82%)	33/39 (85%)
Nodules	12/28 (43%)	4/11 (36%)	16/39 (44%)
Pleural effusion	10/28 (36%)	4/11 (36%)	14/39 (36%)
Pleural mass	1/28 (4%)	0/11 (0%)	1/39 (3)
Consolidation	7/28 (25%)	5/11 (45%)	12/39 (31%)
Cavitation	4/28 (14%)	1/11 (10%)	5/39 (13%)

Table 5. Treatment regimen and mortality.

	Immunosuppressed (n=48)	Immunocompetent (n=18)	Total (n=66)
Treatment regimen, n, (%)			
TMP-SMX	41 (85%)	14(78%)	55(83%)
Linezolid	1(2%)	2(11%)	3(5%)
Amikacin	8(17%)	2(11%)	10(15%)
Carbapenem	18(38%)	5(28%)	23(35%)
Penicillin	4(8%)	1(6%)	5(8%)
Tetracycline	3(6%)	2(11%)	5(8%)
Mortality, n, (%)			
Total mortality	16(33%)	6(33%)	22(33%)
Age < 60 (% of those aged 59 or lower)	8(32%)	1(20%)	9(30%)
Age >59 (% of those aged 60 or older)	8(33%)	5(42%)	13(36%)
Male mortality (% of male individuals)	13(35%)	3(30%)	16(34%)
Female mortality (% of female individuals)	4(36%)	3(38%)	7(37%)
Respiratory failure resulting in mortality (% of individuals with respiratory failure)	14(64%)	6(75%)	20(71%)
Concomitant bacterial infection mortality (% of those with concomitant infection)	3(14%)	1(5%)	4(6%)
Concomitant fungal infection mortality (% of those with concomitant infection)	8(38%)	0	8(12%)
Concomitant CNS disease mortality (% of those with concomitant infection)	2(40%)	2(67%)	4(50%)
Transplant mortality (% of those with transplant)	1(50%)	N/A	1 (50%)
ILD mortality (% of those with disease)	1(50%)	N/A	1(50%)
COPD mortality (% of those with disease	3(33%)	3(75%)	6(46%)

TMP-SMX, trimethoprim-sulfamethoxazole; CNS, central nervous system; ILD, interstitial lung disease; COPD, chronic obstructive pulmonary disease.