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# Invasive Nocardiosis Versus Colonization at a Tertiary Care Center: Clinical and Radiological Characteristics

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## Abstract

**Objective:** To describe the clinical and radiographic findings in a large cohort of patients with positive cultures for *Nocardia* emphasizing the differences between invasive disease and colonization.

**Patients and Methods:** We conducted a single-center, retrospective cohort study of 133 patients with a positive *Nocardia* isolate between August 1, 1998, and November 30, 2018, and a computed tomography (CT) of the chest within 30 days before or after the bacteria isolation date.

**Results:** Patients with colonization were older (71 vs 65 years; $P=.004$), frequently with chronic obstructive pulmonary disease (56.8% vs 16.9%; $P<.001$) and coronary artery disease (47.7% vs 27%, $P=.021$), and had *Nocardia* isolated exclusively from lung specimens (100% vs 83.1%; $P=.003$). On CT of the chest, they had frequent airway disease (84.1% vs 51.7%; $P<.001$). Patients with invasive nocardiosis had significantly ($P<.05$) more diabetes, chronic kidney disease, solid organ transplant, use of corticosteroids, antirejection drugs, and prophylactic sulfa. They had more fever (25.8% vs 2.3%; $P<.001$), cutaneous lesions (14.6% vs 0%; $P=.005$), fatigue (18% vs 0%; $P=.001$), pulmonary nodules (52.8% vs 27.3%; $P=.006$), and free-flowing pleural fluid (63.6% vs 29.4%; $P=.024$). The patterns of nodule distribution were different—diffuse for invasive nocardiosis and peribronchiolar for *Nocardia* colonization.

**Conclusion:** The isolation of *Nocardia* in sputum from a patient with respiratory symptoms does not equal active infection. Only by combining clinical and chest CT findings, one could better differentiate between invasive nocardiosis and *Nocardia* colonization.

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*Nocardia sp* are aerobic, gram-positive, weakly acid-fast, branching actinomycete bacteria found ubiquitous in nature that rarely cause invasive disease in humans (0.33-0.87 cases for every 100,000 people).[1]

Pulmonary nocardiosis is the most common form of invasive disease.[1] However, when *Nocardia* is isolated from respiratory samples, it may not represent invasive nocardiosis. *Nocardia* may colonize the lower airway of patients with chronic lung disease (cystic fibrosis, chronic obstructive pulmonary disease [COPD], bronchiectasis)[2] without causing an invasive disease. In some series, 22.2%-35% patients presenting with a positive *Nocardia* culture had colonization.[3-6] Clinical signs and symptoms of pulmonary nocardiosis can overlap with numerous acute lung diseases. Chest computed tomography (CT) findings in nocardiosis have been described as nonspecific,[2] and preexisting CT lesions (prior nodules, airway disease) could confound the diagnosis of invasive disease. As a result of such diagnostic challenges, when clinical or radiological features cannot independently establish invasive disease, it is necessary to clarify how CT of the chest adds value for differentiating *Nocardia* colonization from invasive nocardiosis.

There is a high mortality rate among immunosuppressed (16%-20%)[7,8] and

immunocompetent (7%) patients with invasive nocardiosis,[9] making prompt and effective treatment imperative. Hence, it is necessary to distinguish between *Nocardia* colonization and invasive nocardiosis before deciding on treatment.

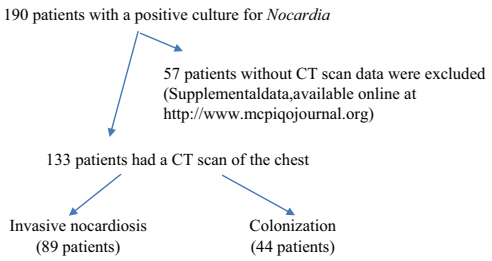
Our study describes the clinical and chest CT radiographic differences of the largest cohort of patients with *Nocardia* colonization published to date, in comparison with characteristics of patients with invasive nocardiosis.

## PATIENTS AND METHODS

A retrospective cohort study at a single tertiary care academic center, Mayo Clinic in Florida, was conducted. The study was approved by Mayo Clinic Institutional Review Board (ID: 17-010028)

We presented the clinical characteristics and outcomes of patients with nocardiosis in a previous article.[7] In the current study, we include the analysis of patients with *Nocardia* colonization, emphasizing their clinical and radiological features.

All microbiology specimens of 190 patients collected between August 1, 1998, and November 30, 2018, that yielded a positive culture for *Nocardia sp*, were reviewed. Only the initial episode of care associated with the first positive *Nocardia* specimen for each patient was considered in our analysis. Medical records and clinical course were reviewed until the previous visit to our institution or the patient's death. *Nocardia* was considered a colonizer if all 4 of the following conditions were met simultaneously: (1) *Nocardia* was isolated from a nonsterile site; (2) either the patient had no clinical symptoms consistent with *Nocardia* infection or an alternative diagnosis was present to explain the initial symptoms; (3) patient did not receive antibiotic treatment at a dose and duration (at least 4 months) recommended for invasive nocardiosis[1]; and (4) the clinical presentation did not change during the follow-up period to warrant a revised diagnosis of invasive nocardiosis. Our study population consisted of 133 patients with either invasive disease (nocardiosis [n=89]) or colonization (n=44) who had a CT scan of the chest 30 days before or 30 days after the positive specimen collection.




### Demographic Characteristics and Clinical Data

Patient demographic characteristics, clinical comorbidities, immune status (white blood cell count and differential, CD4/CD8 count, antirejection therapy use), microbiology data (identification of *Nocardia sp*, antibiotic susceptibility), site of infection, clinical symptoms, and treatment outcomes were obtained from medical records.

### Radiological Data

Computed tomography examinations of the chest (either unenhanced or contrast-enhanced) were obtained throughout the study period on a variety of scanners, with the main technical difference being slice thickness. Two fellowship-trained, experienced chest radiologists (C.A.R., E.M.J.) independently reinterpreted the CT scans obtained at the time of diagnosis and reconciled their differences. Radiologists were blinded to the patient's clinical history, including their immunological status and the presence of other pathogens on cultures. Results were recorded in concordance with the Glossary of Terms publicized by the Fleischner Society in 2008.[10]

Radiological findings were classified in 2 large groups: airway disease and pulmonary parenchymal disease. Airway disease included bronchial wall thickening, bronchial debris, bronchiectasis, and tree-in-bud nodularity. Pulmonary parenchymal disease included nodules and airspace disease. Additional imaging findings reported were the presence of mediastinal or hilar adenopathy, pleural effusion, pleural thickening, chest wall abscess, pericardial effusion, and interstitial lung disease.

### Microbiology Data

Initial determination of "possible *Nocardia sp*" was performed at Mayo Clinic Florida

Microbiology Laboratory. Definitive speciation by 16sDNA sequencing or matrix-assisted laser desorption ionization time-of-flight mass spectrometry and antibiotic susceptibility testing was performed at Mayo Clinic Rochester in Minnesota.

### Statistical Analyses

Continuous variables are summarized with the sample median and range. Categorical variables are summarized with number and percentage of patients. Comparisons of characteristics between the invasive disease and colonization cohorts were made using a Wilcoxon rank sum test (continuous variables) or Fisher exact test (categorical variables). Survival within 1 year after infection (ie, after the date of the first positive specimen) was estimated using the Kaplan-Meier method, in which censoring occurred on the earlier of the date of the previous follow-up or 1 year after infection. Survival after infection was compared between invasive disease and colonized patients using a Cox proportional hazards regression model. *P* values below .05 were considered statistically significant, and all statistical tests were 2-sided. Statistical analyses were performed using SAS (version 9.4; SAS Institute) .

## RESULTS

### Demographic and Clinical Findings

A comparison of the demographic characteristics and risk factors between invasive nocardiosis and *Nocardia* colonization patients is shown in Table 1. Patients who had colonization were older and had a median age of 71 years (range, 50-89 years) at the time of diagnosis vs a median of 65 years (range, 29-86 years) for patients with invasive disease (*P*=.004).

Among preexistent comorbidities, patients with colonization had a higher frequency of COPD (56.8% vs 16.9%; *P*<.001) and coronary artery disease (47.7% vs 27%; *P*=.021). Patients with nocardiosis had a higher frequency of diabetes mellitus (DM) (34.8% vs 11.4%; *P*=.004), and chronic kidney disease (CKD) (32.6% vs 11.4%, *P*=.036). Patients with invasive nocardiosis more frequently were solid organ or bone marrow transplant recipients (52.8% vs 4.5%; *P*<.001), were taking antirejection medications with tacrolimus (48.3% vs 2.3%; *P*<.001) and mycophenolate mofetil (38.2% vs 4.5%; *P*<.001), were more frequently on systemic corticosteroids at the time of admission (69.7% vs 29.5%; *P*<.001), and had taken a high dose of systemic corticosteroids within 6 months before diagnosis (23.6% vs 4.5%, *P*=.007). Patients with invasive disease were more frequently on low dose prophylaxis (160 mg trimethoprim 3 times per week) with trimethoprim-sulfamethoxazole (TMP-SMZ) (15.7% vs 0%; *P*=.005) at the time of diagnosis.

Lungs were the only organs involved in patients with *Nocardia* colonization (100% vs 83.1%; *P*=.003). Other organs such as the skin and soft tissues (18% vs 0%; *P*=.001), brain/cerebrospinal fluid (CSF)/eye (14.6% vs 0%, *P*=.005), or disseminated infection (24.7% vs 0%; *P*<.001) were involved more frequently in patients with invasive disease. Patients with invasive disease had fewer positive sputum/induced sputum/tracheal aspirate (19.1% vs 65.9%; *P*<.001) specimens but more frequently a positive culture from other organs (skin/blood/CSF/brain). Table 2 summarizes the organs and the source of the first specimen.

The incidence of cough, dyspnea, sputum production, or chest pain at presentation was similar in both cohorts. Compared with colonized patients, the invasive group had a higher frequency of fever (25.8% vs 2.3%; *P*<.001), cutaneous lesions (14.6% vs 0%; *P*=.005), and fatigue/generalized weakness (18% vs 0%; *P*=.001) (Table 3).

Survival at 30, 180, and 365 days did not differ between the cohorts. There was no difference regarding treatment failure with need to change antibiotic regimen within 1 year after infection (Table 4). Nocardiosis had a significantly more recent year of infection compared with *Nocardia* colonization (median year of infection 2011 vs 2005; *P*<.001). (Supplemental Figure, available online at http://www.mcpiqojournal.org)

### Radiological Findings

Radiological findings are summarized in Table 5. Of 133 patients, 99 (74.4%) had CT of the chest without intravenous contrast and 34 (25.6%) had CT of the chest with intravenous contrast. Two of the studies with

**TABLE 1. Demographic Characteristics and Risk Factors[a, b]**

| Variable | N | Overall (N=133) | Nocardiosis (n=89) | Colonization (n=44) | *P* value |
|---|---|---|---|---|---|
| Age of first positive specimen (y) | 133 | 67 (29, 89) | 65 (29, 86) | 71 (50, 89) | .004 |
| Sex (male), n (%) | 133 | 77 (57.9) | 53 (59.6) | 24 (54.5) | .71 |
| Alcohol abuse, n (%) | 133 | 5 (3.8) | 2 (2.2) | 3 (6.8) | .33 |
| Intravenous drug use, n (%) | 133 | 1 (0.8) | 1 (1.1) | 0 (0.0) | >.99 |
| Diabetes, n (%) | 133 | 36 (27.1) | 31 (34.8) | 5 (11.4) | .004 |
| CKD, n (%) | 132 | | | | .036 |
| No CKD | | 99 (74.4) | 60 (67.4) | 39 (88.6) | |
| Any CKD | | 16 (12.0) | 14 (15.7) | 2 (4.5) | |
| ESRD on dialysis | | 18 (13.5) | 15 (16.9) | 3 (6.8) | |
| Coronary artery disease, n (%) | 133 | 45 (33.8) | 24 (27.0) | 21 (47.7) | .021 |
| COPD, n (%) | 133 | 40 (30.1) | 15 (16.9) | 25 (56.8) | <.001 |
| Liver cirrhosis, n (%) | 133 | 7 (5.3) | 4 (4.5) | 3 (6.8) | .68 |
| Hematologic malignancy, n (%) | 133 | 12 (9.0) | 7 (7.9) | 5 (11.4) | .53 |
| Chemotherapy 6 mos before diagnosis, n (%) | 133 | 8 (6.0) | 6 (6.7) | 2 (4.5) | >.99 |
| Rheumatologic disease on immunosuppressive therapy, n (%) | 133 | 14 (10.5) | 12 (13.5) | 2 (4.5) | .14 |
| Transplant (SOT and BMT) | 133 | 49 (36.8) | 47 (52.8) | 2 (4.5) | <.001 |
| Previous trauma/operation of the infected site | 133 | 5 (3.8) | 4 (4.5) | 1 (2.3) | >.99 |
| High corticosteroid dose 6 mos before diagnosis[c] | 133 | 23 (17.3) | 21 (23.6) | 2 (4.5) | .007 |
| Hypogammaglobulinemia before diagnosis | 133 | 8 (6.0) | 6 (6.7) | 2 (4.5) | >.99 |
| Low CD4 count before diagnosis[d] | 133 | 16 (12.0) | 14 (15.7) | 2 (4.5) | .088 |
| Low CD8 count before diagnosis[e] | 132 | 7 (5.3) | 7 (8.0) | 0 (0.0) | .095 |
| TMP-SMX prophylaxis at diagnosis | 132 | 14 (10.6) | 14 (15.7) | 0 (0.0) | .005 |
| Corticosteroids | 133 | 75 (56.4) | 62 (69.7) | 13 (29.5) | <.001 |
| Cyclosporine, n (%) | 132 | 2 (1.5) | 1 (1.1) | 1 (2.3) | >.99 |
| Tacrolimus, n (%) | 133 | 44 (33.1) | 43 (48.3) | 1 (2.3) | <.001 |
| Azathioprine, n (%) | 133 | 3 (2.3) | 3 (3.4) | 0 (0.0) | .55 |
| Mycophenolate mofetil, n (%) | 133 | 36 (27.1) | 34 (38.2) | 2 (4.5) | <.001 |
| Sirolimus, n (%) | 132 | 1 (0.8) | 1 (1.1) | 0 (0.0) | >.99 |
| Other immunosuppressive medications, n (%)[f] | 133 | 7 (5.3) | 6 (6.7) | 1 (2.3) | .42 |
| All immunosuppressive medications, n (%)[g] | 132 | 56 (42.4) | 52 (58.4) | 4 (9.3) | <.001 |

[a]BMT, bone marrow transplant; COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease; SOT, solid organ transplant; TMP-SMX, trimethoprim-sulfamethoxazole.
[b]The sample median (minimum, maximum) is given for continuous variables. *P* values comparing invasive vs noninvasive patients result from a Wilcoxon rank sum test (continuous variables) or Fisher exact test (categorical variables).
[c]High dose of steroids: daily prednisone equivalent of 20 mg for >1 month.
[d]CD4 cell count below 500 cells/mm$^3$.
[e]CD8 cell count below 150 cells/mm$^3$.
[f]Mercaptopurine, rituximab, bevacizumab, combination chemotherapy.
[g]Cyclosporine, tacrolimus, azathioprine, mycophenolate mofetil, sirolimus, or other immunosuppressive medications.

intravenous contrast, 1 for each cohort of patients, were CT angiography with pulmonary emobolism protocol. The pulmonary parenchymal disease (nodules and airspace disease/consolidation), airway disease, and additional findings were all present in both cohorts with various frequencies.

**Invasive Disease: Nocardiosis.** The predominant imaging feature in invasive nocardiosis was the presence of pulmonary parenchymal abnormalities, with 60.7% of the patients presenting with airspace disease and 52.8% with nodules. Airspace disease was most frequently seen as multiple subsegmental areas of

**TABLE 2. Specimen Source and Infection Site[a]**

| Variable | N | Overall (N=133), n (%) | Nocardiosis (n=89), n (%) | Colonization (n=44), n (%) | *P* value |
|---|---|---|---|---|---|
| First specimen source | | | | | |
| Bronchoalveolar lavage/brushing | 133 | 54 (40.6) | 39 (43.8) | 15 (34.1) | .35 |
| Sputum/induced sputum/tracheal aspirate | 133 | 46 (34.6) | 17 (19.1) | 29 (65.9) | <.001 |
| Pleural fluid | 133 | 3 (2.3) | 3 (3.4) | 0 (0.0) | .55 |
| Lung biopsy | 133 | 7 (5.3) | 7 (7.9) | 0 (0.0) | .095 |
| Abscess/solid organ biopsy | 133 | 1 (0.8) | 1 (1.1) | 0 (0.0) | >.99 |
| Cutaneous biopsy/swab/skin abscess | 133 | 13 (9.8) | 13 (14.6) | 0 (0.0) | .005 |
| Blood culture | 133 | 5 (3.8) | 5 (5.6) | 0 (0.0) | .17 |
| Cerebrospinal fluid culture | 133 | 1 (0.8) | 1 (1.1) | 0 (0.0) | >.99 |
| Brain abscess biopsy | 133 | 3 (2.3) | 3 (3.4) | 0 (0.0) | .55 |
| Synovial fluid/joint aspirate | 133 | 0 (0.0) | 0 (0.0) | 0 (0.0) | >.99 |
| Other[b] | 133 | 1 (0.8) | 1 (1.1) | 0 (0.0) | >.99 |
| Organs from where specimens were collected | | | | | |
| Disseminated infection[c] | 133 | 22 (16.5) | 22 (24.7) | 0 (0.0) | <.001 |
| Lung | 133 | 118 (88.7) | 74 (83.1) | 44 (100.0) | .003 |
| Skin and soft tissue | 133 | 16 (12.0) | 16 (18.0) | 0 (0.0) | .001 |
| Brain/cerebrospinal fluid /eye | 133 | 13 (9.8) | 13 (14.6) | 0 (0.0) | .005 |
| Joint | 133 | 2 (1.5) | 2 (2.2) | 0 (0.0) | >.99 |
| Other[d] | 133 | 3 (2.3) | 3 (3.4) | 0 (0.0) | .55 |

[a]*P* values comparing invasive vs noninvasive patients result from Fisher exact test.
[b]Peritoneal fluid.
[c]Infection involving 2 or more noncontiguous organs, presence of bacteremia.
[d]Salivary gland, peritoneum, kidney explant site abscess.

consolidation with peripheral (94.4%) and lower lung zone (70.4%) distribution. One-third (33.3%) of these areas of airspace consolidation had central cavitation/necrosis. Nodules were almost twice as frequent in patients with invasive nocardiosis (47 [52.8%]) compared with the colonization group (12 [27.3%]; *P*=.006). These nodules were commonly multiple (78.7%), solid (85.1%), and smaller than 3 cm (74.5%) with a random pattern of distribution in 70% of cases compatible with hematogenous dissemination. Central cavitation was observed in 19.1% of nodules, and 10.6% had a halo sign. Nodules with cavitation were present in both cohorts, predominantly in patients with invasive disease; however, the difference did not achieve statistical significance (9 [19.1%] vs 1 [8.3%]; *P*=.37). The cavitated nodule observed in the colonization cohort was present in 1 patient successfully treated for pulmonary cryptococcosis.

Imaging findings of airway disease were present in 51.7% of patients with invasive nocardiosis, statistically significantly lower than the colonization cohort (*P*<.001).

Pleural effusion was seen in 80% of the patients with invasive disease and adenopathy in 54.5%. One case (1.8%) of invasive disease presented with chest wall extension (empyema necessitans). The presence of a pleural effusion was statically higher in the invasive nocardiosis group (80% vs 41.2%).

**Nocardia Colonization.** The predominant imaging feature in colonized patients was airway disease, reaching statistical significance compared with the invasive group (84.1% vs 51.7%; *P*<.001). Airway disease in this group was characterized by airway thickening (89.2%), bronchiectasis (67.6%), endobronchial debris (62.2%), and tree-in-bud nodularity in 59.5% of patients. The patients colonized with *Nocardia* also presented with nodules (27.3% of patients), but at a significantly lower frequency than the one seen in patients with invasive nocardiosis. When nodules were present in the colonization


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**TABLE 3. Clinical Symptoms on Admission[a]**

| Clinical symptoms | N | Overall (N=133), n (%) | Nocardiosis (n=89), n (%) | Colonization (n=44), n (%) | *P* value |
|---|---|---|---|---|---|
| Cough | 133 | 74 (55.6) | 45 (50.6) | 29 (65.9) | .10 |
| Dyspnea | 133 | 59 (44.4) | 38 (42.7) | 21 (47.7) | .71 |
| Sputum production | 133 | 40 (30.1) | 25 (28.1) | 15 (34.1) | .55 |
| Fever | 133 | 24 (18.0) | 23 (25.8) | 1 (2.3) | <.001 |
| Cutaneous lesions | 133 | 13 (9.8) | 13 (14.6) | 0 (0.0) | .005 |
| Asthenia | 133 | 16 (12.0) | 16 (18.0) | 0 (0.0) | .001 |
| Chills | 133 | 15 (11.3) | 13 (14.6) | 2 (4.5) | .14 |
| Chest pain | 133 | 11 (8.3) | 9 (10.1) | 2 (4.5) | .34 |
| Weight loss | 133 | 7 (5.3) | 7 (7.9) | 0 (0.0) | .095 |
| Focal neurological signs | 133 | 6 (4.5) | 6 (6.7) | 0 (0.0) | .18 |

[a]*P* values comparing invasive vs noninvasive patients result from Fisher exact test. Additional signs and symptoms present in <3 patients included salivary gland enlargement, abdominal pain, hypotension, wheezing, hemoptysis, confusion, headache, seizures, coma, and arthritis.

group, most (67%) had centrilobular distribution suggesting endobronchial spread. Airspace disease was present in 43.2% of patients with noninvasive disease, less frequently compared with the invasive group.

Approximately 41.2% of this group of patients had pleural effusion and 64.7% had adenopathy. In contrast to the invasive nocardiosis cohort, no patient in this group presented with chest wall extension of the infection.

## DISCUSSION

Distinguishing invasive *Nocardia sp* infection from colonization could be a challenging task even for an infectious disease specialist. Sometimes, patient's prior medical history and clinical presentation may not be sufficient to establish the diagnosis of infection, and chest CT scan is used as adjunct for diagnosis. Combining clinical and radiological information may give clinicians the armamentarium needed to define the infectious status of their patients. We analyzed a large number of patients with positive cultures for *Nocardia sp* and re-examined CT scans of the chest for specific findings that allowed us to differentiate between invasive disease and colonization.

Patients' underlying comorbidities are the most important clinical determinant of invasive infection. Historically, invasive nocardiosis has been an infection of patients with impaired immunity. We found a similar association: solid organ transplant recipients on antirejection medications and patients with other conditions associated with low immunity, such as DM and CKD were diagnosed with invasive nocardiosis. In addition, we also confirmed that patients with chronic lung disease and COPD more frequently had colonization.[6]

Symptoms at presentation are the next element used to diagnose invasiveness. The frequency of respiratory symptoms such as

**TABLE 4. Treatment Failure and Survival[a]**

| Characteristic | N | Overall (N=133) | Nocardiosis (n=89) | Colonization (n=44) | *P* value |
|---|---|---|---|---|---|
| Treatment failure with need to change antibiotic | 133 | 1 (0.8%) | 1 (1.1%) | 0 (0.0%) | >.99 |
| Survival after infection, % (95% CI) | 133 | | | | .12 |
| 30 d | | 94.7 (91.0-98.6) | 92.1 (86.7-97.9) | 100.0 (0.0-100.0) | |
| 180 d | | 82.7 (76.5-89.4) | 79.8 (71.9-88.6) | 88.6 (79.7-98.5) | |
| 1 y | | 75.9 (69.0-83.6) | 71.9 (63.1-81.9) | 84.1 (73.8-95.6) | |

[a]*P* values comparing invasive vs noninvasive patients result from Fisher exact test (treatment failure with need to change antibiotic) or an unadjusted Cox proportional hazards regression model (survival after infection).

**TABLE 5. Radiology Findings[a]**

| Variable | N | Overall (N=133), n (%) | Nocardiosis (n=89), n (%) | Colonization (n=44), n (%) | *P* value |
|---|---|---|---|---|---|
| **Nodules** | 133 | 59 (44.4) | 47 (52.8) | 12 (27.3) | .006 |
| Nodules count | 59 | | | | .72 |
| Single | | 12 (20.3) | 10 (21.3) | 2 (16.7) | |
| Multiple | | 47 (79.7) | 37 (78.7) | 10 (83.3) | |
| Nodule craniocaudal distribution | | | | | |
| Upper | 59 | 32 (54.2) | 29 (61.7) | 3 (25.0) | .023 |
| Mid | 59 | 38 (64.4) | 31 (66.0) | 7 (58.3) | .62 |
| Lower | 59 | 34 (57.6) | 26 (55.3) | 8 (66.7) | .48 |
| Nodule axial distribution | | | | | |
| Central | 59 | 23 (39.0) | 18 (38.3) | 5 (41.7) | .83 |
| Peripheral | 59 | 53 (89.8) | 42 (89.4) | 11 (91.7) | .81 |
| Nodule size, cm | | | | | |
| <1 | 59 | 32 (54.2) | 25 (53.2) | 7 (58.3) | .75 |
| 1-3 | 59 | 29 (49.2) | 23 (48.9) | 6 (50.0) | .95 |
| >3 | 59 | 14 (23.7) | 12 (25.5) | 2 (16.7) | .52 |
| Nodule density | | | | | |
| Solid | 59 | 51 (86.4) | 40 (85.1) | 11 (91.7) | .55 |
| Ground glass | 59 | 9 (15.3) | 6 (12.8) | 3 (25.0) | .29 |
| Mixed | 59 | 2 (3.4) | 2 (4.3) | 0 (0.0) | .47 |
| Nodule pattern of distribution | | | | | |
| Random | 59 | 23 (39.0) | 21 (44.7) | 2 (16.7) | .076 |
| Centrilobular | 59 | 13 (22.0) | 9 (19.1) | 4 (33.3) | .29 |
| Nodule shape | | | | | |
| Round | 59 | 35 (59.3) | 28 (59.6) | 7 (58.3) | .94 |
| Irregular | 59 | 19 (32.2) | 14 (29.8) | 5 (41.7) | .43 |
| Lobulated | 59 | 28 (47.5) | 23 (48.9) | 5 (41.7) | .65 |
| Nodule additional features | | | | | |
| Cavitation | 59 | 10 (16.9) | 9 (19.1) | 1 (8.3) | .37 |
| Halo sign | 59 | 5 (8.5) | 5 (10.6) | 0 (0.0) | .24 |
| Reverse halo | 59 | 0 (0.0) | 0 (0.0) | 0 (0.0) | >.99 |
| **Airspace disease** | 133 | 73 (54.9) | 54 (60.7) | 19 (43.2) | .066 |
| Airspace disease pattern | | | | | |
| Consolidation | 73 | 64 (87.7) | 46 (85.2) | 18 (94.7) | .43 |
| Ground glass | 73 | 27 (37.0) | 21 (38.9) | 6 (31.6) | .78 |
| Airspace disease number | 73 | | | | .59 |
| Single | | 29 (39.7) | 20 (37.0) | 9 (47.4) | |
| Multiple | | 44 (60.3) | 34 (63.0) | 10 (52.6) | |
| Airspace disease craniocaudal distribution | | | | | |
| Upper | 73 | 34 (46.6) | 29 (53.7) | 5 (26.3) | .061 |
| Mid | 73 | 29 (39.7) | 25 (46.3) | 4 (21.1) | .062 |
| Lower | 73 | 53 (72.6) | 38 (70.4) | 15 (78.9) | .56 |
| Airspace disease axial distribution | | | | | |
| Central | 73 | 25 (34.2) | 21 (38.9) | 4 (21.1) | .26 |
| Peripheral | 73 | 70 (95.9) | 51 (94.4) | 19 (100.0) | .56 |
| Airspace disease distribution level | | | | | |
| Subsegmental | 73 | 50 (68.5) | 37 (68.5) | 13 (68.4) | >.99 |
| Segmental | 73 | 22 (30.1) | 17 (31.5) | 5 (26.3) | .78 |
| Lobar | 73 | 15 (20.5) | 11 (20.4) | 4 (21.1) | >.99 |
| Airspace disease additional features | | | | | |
| Necrosis/cavitation | 73 | 23 (31.5) | 18 (33.3) | 5 (26.3) | .78 |
| Bronchograms | 73 | 24 (32.9) | 20 (37.0) | 4 (21.1) | .26 |

*Continued on next page*



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**TABLE 5. Continued**

| Variable | N | Overall (N=133), n (%) | Nocardiosis (n=89), n (%) | Colonization (n=44), n (%) | *P* value |
|---|---|---|---|---|---|
| **Airway disease** | 133 | 83 (62.4) | 46 (51.7) | 37 (84.1) | <.001 |
| Airway disease features | | | | | |
| Bronchial wall thickening | 83 | 70 (84.3) | 37 (80.4) | 33 (89.2) | .37 |
| Bronchial debris | 83 | 49 (59.0) | 26 (56.5) | 23 (62.2) | .66 |
| Bronchiectasis | 83 | 50 (60.2) | 25 (54.3) | 25 (67.6) | .26 |
| Tree-in-bud nodularity | 83 | 46 (55.4) | 24 (52.2) | 22 (59.5) | .66 |
| **Additional findings** | 133 | 72 (54.1) | 55 (61.8) | 17 (38.6) | .016 |
| Adenopathy | 72 | 41 (56.9) | 30 (54.5) | 11 (64.7) | .58 |
| Free-flowing pleural effusion | 72 | 40 (55.6) | 35 (63.6) | 5 (29.4) | .024 |
| Loculated pleural effusion | 72 | 11 (15.3) | 9 (16.4) | 2 (11.8) | >.99 |
| Pleural thickening/enhancement | 72 | 17 (23.6) | 14 (25.5) | 3 (17.6) | .75 |
| Chest wall involvement "empyema necessitates" (bone/muscle) | 72 | 1 (1.4) | 1 (1.8) | 0 (0.0) | >.99 |
| Pericardial effusion | 72 | 3 (4.2) | 2 (3.8) | 1 (5.3) | .56 |

[a]The sample median (minimum, maximum) is given for continuous variables. *P* values comparing invasive vs noninvasive patients result from a Wilcoxon rank sum test (continuous variables) or Fisher exact test (categorical variables).

cough, dyspnea, sputum production, and chest pain was not different between our cohorts, and it was not helpful to differentiate the diagnosis. However, systemic symptoms with fever, fatigue, and cutaneous lesions were more frequent in patients with invasive nocardiosis.

Patients with invasive disease were more frequently taking low-dose TMP-SMZ (15.7% vs 0%; *P*=.005) for prophylaxis at the time of diagnosis. Prescription of a low dose of TMP-SMX for *Pneumocystis jirovecii* prophylaxis was common in our immunosuppressed, solid organ recipient patients on antirejection medications.[7] Nocardia infection was previously shown to breakthrough this low dose prophylaxis.[7,9] Therefore, the diagnosis of invasive Nocardia infection should not be ruled out in patients receiving low-dose TMP-SMZ prophylaxis for other reasons.

As previously described,[6] positive extrapulmonary specimens are highly suggestive of invasive nocardiosis. Our invasive cohort frequently had a positive *Nocardia sp* culture isolated from tissues other than lungs (skin/blood/CSF/solid organ), suggesting disseminated disease.

It is often uncertain in many cases whether the specimen isolation of *Nocardia* is related to airway colonization or to a more advanced disease process with involvement of the alveolar epithelium. Airway abnormalities on CT, such as bronchial wall thickening, bronchial debris, bronchiectasis, and tree-in-bud nodularity, were more commonly seen in colonized patients. Conversely, imaging findings of pulmonary parenchymal involvement, such as nodules and airspace disease (ground glass opacities and airspace consolidation), were more commonly seen in patients with invasive nocardiosis. Considering that most patients from the invasive disease cohort were also immunosuppressed, our findings correlate for the most part with other studies that have evaluated differences in radiological patterns in patients with pulmonary nocardiosis. Blackmon et al,[11] Chen et al,[12] and Sterinbrink et al[9] noted a higher presence of nodules and nodules with cavitation in immunosuppressed patients than in immunocompetent ones. In our cohort, nodules were found more frequent in patients with invasive nocardiosis than in those with colonization; however, nodule cavitation, although more common in invasive disease, did not reach statistical significance. Nodules with cavitation and cavitated airspace disease were present in 16.9% and 31.5% of patients, respectively, both being predominant in those with invasive disease, but the difference did not reach statistical significance. In previous studies, the frequency of cavitated nodules/masses or

consolidations ranged between 6.9% and 76%.[8,12,13] Possible explanations for such wide variation may be differences in imaging protocols (including imaging spatial resolution/slice thickness and the administration of intravenous contrast, which can allow for improved visualization of areas of cavitation/necrosis), timing of imaging with respect of diagnosis and initiation of therapy, and the relatively small number of patients in each study.

The presence of pulmonary nodules on CT of the chest does not always indicate invasive nocardiosis. Nodules have been observed in patients with *Nocardia* colonization.[14] However, the pattern of distribution of lung nodules plays a more important role in diagnosis. Fujita et al[5] noted a higher frequency of centrilobular nodules in immunocompetent patients than in immunocompromised ones. The pattern of spread was different between our 2 groups, with 70% of invasive cases following a random pattern—as seen in hematogenous spread of disease—whereas 67% of cases in the colonization group followed a centrilobular pattern.[15,16]

The presence of pleural effusion on the CT scan pointed to the presence of invasive disease as opposed to colonization. Invasive infections trigger a more robust local inflammatory response and frequently extend to the periphery of the lung, leading to an infected effusion or parapneumonic effusion.

The association of chronic lung conditions and bronchial structural abnormalities with pulmonary nocardiosis seems to be a complex one. We found that CT scan findings of airway disease (bronchiectasis, bronchial wall thickening and debris) were present in both cohorts but were significantly more frequent in patients with colonization. Margalit et al[6] and Margalit et al[17] found the preexistence of pulmonary disease to be the determining factor for colonization and the treatment with systemic corticosteroids to be more frequently associated with invasive nocardiosis. A possible explanation is that patients with prior bronchial diseases and/or COPD and impaired mucus clearance would initially develop *Nocardia* colonization. Once exposed to immunosuppressive agents with either prolonged systemic corticosteroid therapy or antirejection medications, those patients would develop pulmonary nocardiosis. It is unclear under what circumstances (dose of immunosuppressants, duration of therapy) and what percentage of patients with bronchial disease and *Nocardia* colonization will develop invasive nocardiosis when exposed to immunosuppression. A prospectively designed study could address this question.

Survival rate at 1 year in patients with invasive disease was comparable with the results obtained in studies with larger cohorts.[7,8] Interestingly, the survival rates were not significantly higher in patients with colonization. Older age and frequent chronic comorbidities (COPD, coronary artery disease) in patients in this cohort were probably responsible for their lower survival rate.[18]

## STUDY LIMITATIONS

The main limitation of our study was the retrospective design, which may have introduced a data collection bias. Although the sample size was large compared with the previously published series, it was still relatively small from a statistical standpoint. Therefore, the possibility of a type II error (ie, a false-negative finding) is important to consider.

Because of its retrospective design, our study was also at risk for sampling bias. It is likely that immunosuppressed patients with a positive respiratory isolate would have been included in the invasive disease cohort, and patients with a chronic lung condition would have been included in the colonized cohort. In our definition of invasive disease, we used the minimum effective duration of antibiotic therapy as recommended by expert opinion. If a shorter duration would have been effective for invasive nocardiosis therapy, some colonized patients could have been misclassified (another possible sampling bias). The patients were closely followed up after the initial diagnosis for any change in disease classification (ie, colonized patients misclassified as infected and vice versa) to mitigate this unavoidable bias.

The 2 independent radiologists who reviewed the CT scans were unaware of patients' clinical characteristics but were aware of the cohort that the patients belonged to. We believe that having the images independently reviewed and reconciled after


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consensus was reached partially mitigated this limitation.

## CONCLUSION

Although most patients who have *Nocardia sp* isolated from a respiratory specimen will end up having an invasive disease, a significant proportion could only be colonized with this bacterium. A CT of the chest can be helpful to differentiate between invasive nocardiosis and *Nocardia* colonization.

The presence of nodules, airspace disease with varying degrees of cavitation and pleural effusion found on CT scan of the chest, in younger patients receiving immunosuppressive agents, with CKD and DM, and presenting with systemic symptoms in addition to respiratory symptoms are highly suggestive of invasive nocardiosis.

Preexistent airway disease, peribronchial and "tree-in-bud" nodule distribution in older patients with COPD, presenting mainly with respiratory symptoms and having no extrapulmonary *Nocardia* isolates suggests the diagnosis of *Nocardia* colonization.

Despite the findings described in this study, no specific radiographic pattern on the CT of the chest is pathognomonic of invasive nocardiosis. The clinician should use patient characteristics and underlying conditions and the radiographic findings on the CT scan to distinguish between *Nocardia* colonization and invasive infection. Nocardia infection should not be ruled out in individuals receiving TMP-SMZ prophylaxis.

The risk factors for progression and the rate of progression of *Nocardia* colonization to invasive nocardiosis are unknown. Once recognized, colonized patients could receive antibiotic prophylaxis to prevent conversion to nocardiosis. However, because of the low incidence of invasive nocardiosis even in immunosuppressed patients, antibiotic prophylaxis for every colonization case may unnecessarily treat a large population. A prospective study is needed to identify appropriate patients with *Nocardia* colonization who should start prophylaxis against invasive nocardiosis.

## POTENTIAL COMPETING INTERESTS

The authors report no competing interests.

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## SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mcpiqojournal.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

**Abbreviations and Acronyms:** **CKD**, chronic kidney disease; **COPD**, chronic obstructive pulmonary disease; **CSF**, cerebrospinal fluid; **CT**, computed tomography; **DM**, diabetes mellitus; **TMP-SMZ**, trimethoprim-sulfamethoxazole

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