ORIGINAL ARTICLE

Pulmonary Nocardiosis Presenting as Exacerbation of Chronic Pulmonary Disease

Roopa Kancherla[1], Ramanathan Palaniappan Ramanathan[2], Bobbe Appalaraju[3], Srinivas Rajagopala[4]

Abstract

Background: Pulmonary nocardiosis (PN) occurs in chronic pulmonary disease (CPD) in the absence of traditional risk factors. Clinical features that differentiate bacterial exacerbations (AE-CPD_b) from PN-related exacerbations (AE-CPD_{PN}) are not well described.

Objectives: To describe a series of AE-CPD_{PN} without traditional risk factors and compare clinical features, radiology and outcomes with age, gender and CLD-type matched AE-CPD_b.

Materials and methods: Single-center retrospective review and case-control study.

Results: AE-CPD_{PN} had longer duration of symptoms and more leukocytosis at hospitalization. AE-CPD_b patients were sicker with more chronic respiratory failure (OR 33.3, $p = 0.01$), cardiac disease and pulmonary hypertension (OR 6.2, $p = 0.008$) at diagnosis. More patients with AE-CPD_b were discharged on domiciliary oxygen (OR 5.27, $p = 0.01$). On logistic regression, AE-CPD_{PN} was independently associated with mechanical ventilation (OR 22.3, $p = 0.01$), length of hospital stay (median difference, 4 days, $p = 0.016$) but not to hospital mortality. 22.7% of AE-CPD_{PN} died. Respiratory failure requiring oxygen, NIPPV or mechanical ventilation was associated with mortality in AE-CPD_{PN}.

Conclusion: PN is a rare cause of AE-CPD and can be suspected by longer symptom duration, more leukocytosis, consolidation and cavitation. AE-CPD_{PN} is associated with longer hospital stay and mechanical ventilation. Respiratory failure is associated with mortality in AE-CPD_{PN}.

Key messages:

- Pulmonary nocardiosis can present in advanced chronic lung disease as an exacerbation in the absence of traditional risk factors like immunosuppression.
- Bronchiectasis, followed by chronic obstructive pulmonary disease are the most common chronic lung disease risk factors.
- Pulmonary nocardiosis is a rare cause of acute exacerbation of chronic pulmonary disease (CPD).
- Compared to exacerbations of CPD due to bacterial infections, nocardiosis-related exacerbations (CPD_{PN}) were independently related to need for mechanical ventilation and length of hospital stay.
- Respiratory failure requiring oxygen, noninvasive ventilation and mechanical ventilation are associated with mortality in AE-CPD_{PN}.

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Introduction

Acute exacerbation of chronic pulmonary disease (AE-CPD) leads to substantial worsening in quality of life, need for additional therapies, morbidity, mortality and costs.[1] Severe exacerbations are associated with respiratory failure, need for mechanical ventilation and mortality.[2] Pulmonary nocardiosis, the most frequent presentation of human infection by *Nocardia* spp, is increasingly being recognized in patients with CPDs, including chronic obstructive pulmonary disease (COPD).[3] Predisposing factors include bacterial colonization of lower airways with advanced lung disease, oral steroid use for exacerbations and structural lung disease in the form of associated bronchiectasis in severe COPD.[4] Most series of PN in CPDs include patients with associated traditional predisposing factors like steroid therapy, solid-organ or hematopoietic cell transplantation, human immunodeficiency virus infection or malignancy; mortality determinants were thus affected by these associated risk factors.[4] The clinical features, radiologic findings, laboratory clues that should suggest the presence of PN in AE-CPD (AE-CPD_{PN}) and its outcomes are not well described. We describe a series of AE-CPD_{PN} in the absence of traditional risk factors to determine clinical features that can distinguish it from bacterial exacerbations of CPD (AE-CPD_b) and determine the association of AE-CPD_{PN} with need for mechanical ventilation, hospital length of stay and mortality.

[1,2,4]Department of Pulmonology, PSG Institute of Medical Sciences and Research, Peelamedu, Coimbatore, Tamil Nadu, India

[3]Department of Microbiology, PSG Institute of Medical Sciences and Research, Peelamedu, Coimbatore, Tamil Nadu, India

Corresponding Author: Srinivas Rajagopala, Department of Pulmonology, PSG Institute of Medical Sciences and Research, Peelamedu, Coimbatore, Tamil Nadu, India, Phones: 91-422-2570170, 91-422-2598822, e-mail: visitsrinivasan@gmail.com

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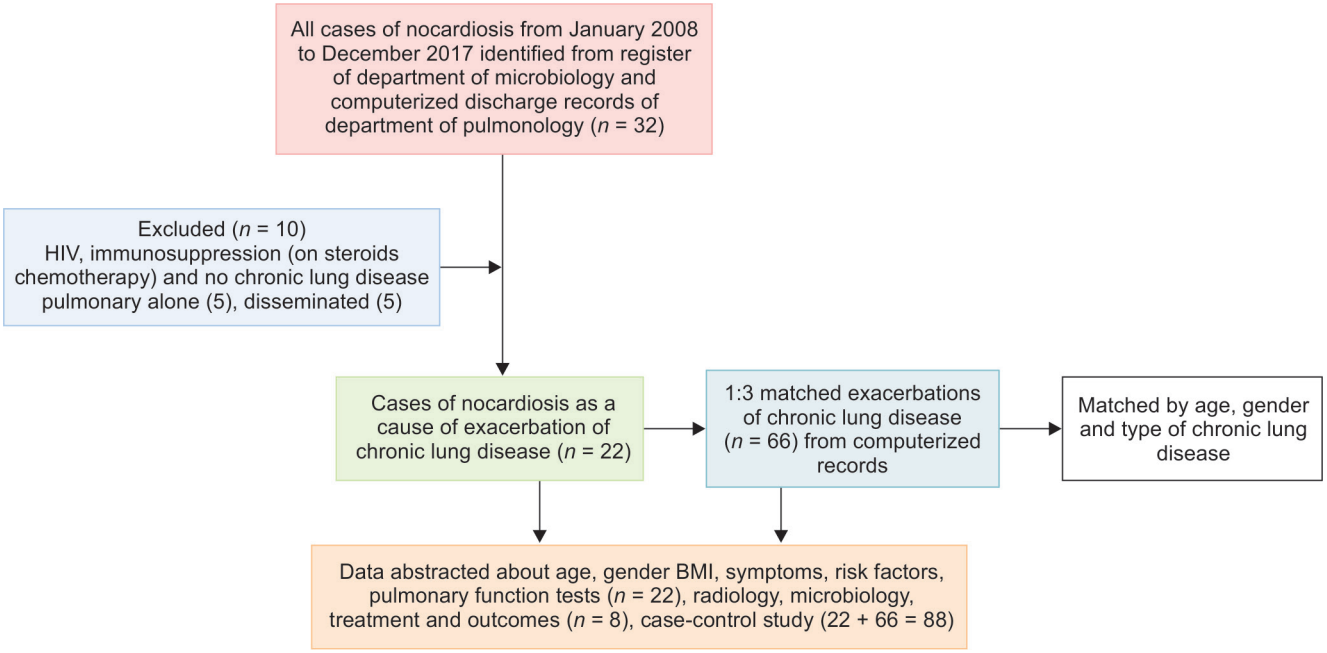
Materials and Methods

This is a retrospective study of patients ≥18 years and a final diagnosis of PN and AE-CPD from a large tertiary care hospital in southern India over 10 years between January 2008 and December 2017. All cases with PN were identified by an electronic search of our records and cross-referenced by a simultaneous manual search of the nocardiosis register in the department of microbiology. Clinical records of all identified cases were retrieved. Only PN presenting

Flowchart 1: Number of enrolled patients in the study



with worsening of underlying CPD was included. PN associated with long-term steroid therapy, immunosuppressive therapy, human immunodeficiency infection (HIV) and malignancy and PN in the absence of CPD was excluded (Flowchart 1).

Study Subjects

Case Series

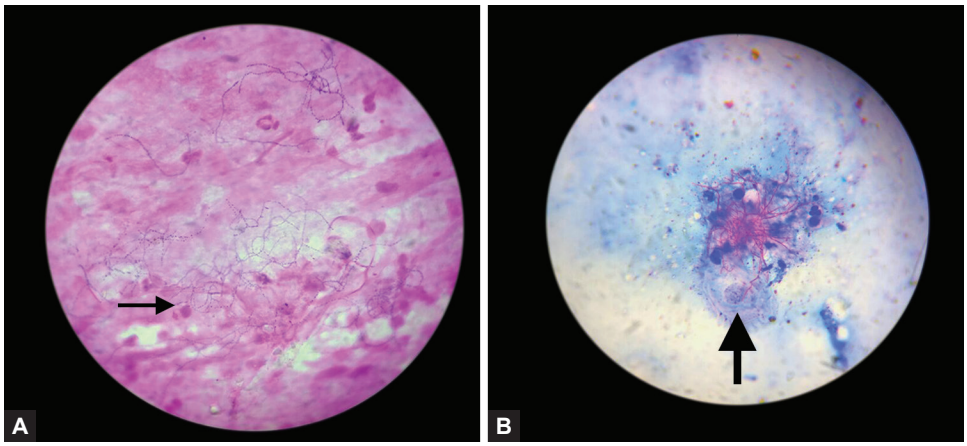
CPD was defined by the presence of one of the following conditions; COPD, bronchial asthma, bronchiectasis, interstitial lung disease (ILD) and post-tuberculosis lung disease. The diagnosis of COPD, bronchial asthma, bronchiectasis and ILD was made according to standard guidelines.[1,5,6] The diagnosis of obstruction and restriction on spirometry was according to ATS/ERS guidelines.[7] An exacerbation of CPD was defined as worsening of respiratory symptoms that resulted in additional therapy.[1] If the initial diagnosis of CPD was made during an exacerbation of CPD, spirometry performed subsequently during stable disease, where available, was taken for data abstraction. PN was diagnosed on the basis of (i) presence of compatible respiratory symptoms and (ii) isolation of *Nocardia* spp. in smears and/or cultures of respiratory samples or (iii) histopathology of transthoracic or bronchoscopic biopsies showing organisms consistent with *Nocardia* spp.[8] Respiratory samples included sputum, endotracheal aspirates, bronchoalveolar lavage fluid (BALF) and pleural fluid. Nocardiosis was diagnosed as "disseminated" if there was isolation in blood culture or demonstrable infection in other organs, including skin and central nervous system in association with respiratory infection.[8] Recent steroid intake was defined as steroid intake in the 3 months prior to diagnosis of PN. We excluded any patient with steroid intake >7.5 mg in 3 months prior to the diagnosis of pulmonary nocardiosis to eliminate oral steroid as a confounding factor for AE-$CPD_{PN.}$ Chronic respiratory failure was defined by an arterial blood gas (ABG) with PaO_2 ≤55 mm Hg or <60 mm Hg in the presence of pulmonary hypertension; $PaCO_2$ ≥45 mm Hg with or without pH ≤7.36 in the absence of symptoms suggestive of an acute deterioration.[1,9]

Controls

Controls were patients with COPD, bronchiectasis, post-tuberculosis lung disease and ILD without any Immunocompromising condition, including receipt of steroids in 3 months prior to study inclusion. Only exacerbations that were microbiologically proven or clinically presumed to be due to bacterial infection (AE-CPD_b) were included. Receipt of antibiotics was taken as a surrogate for clinical presumption of infection; any controls with suspected or proven exacerbations due to viral infections, heart failure or pulmonary embolism were excluded. Patients with a presumed bacterial infection were included only if they had a complete clinical response to antibiotics and supportive care alone; outpatient follow-up notes and radiology were retrieved and reviewed for all controls for confirmation. Controls with exacerbations and radiological infiltrates were included in an attempt to match illness severity between cases and controls. Three controls were identified for each case and matched by age, gender and type of chronic lung disease.

Microbiological Identification

Samples collected included sputum, endotracheal aspirates, BALF and pleural fluid under sterile precautions. The samples were examined by direct microscopy after Gram's staining to establish specimen quality. Modified Kinyoun's stain was also done if nocardiosis was suspected clinically or if Gram's stain showed organisms compatible with *Nocardia* spp. All samples were then homogenized with sterile glass beads in a test tube and incubated in blood agar and Sabouraud's dextrose agar at 37°C in an aerobic atmosphere for up to 4 weeks and examined every alternate day for growth. The presumptive identification of *Nocardia* spp. was based on the microscopy showing branching gram-positive thin filamentous rods (Fig. 1A), partially acid-fast with modified Kinyoun's stain (Fig. 1B) and the macroscopic morphology of buff or pigmented waxy cerebriform colonies. Identification at the species level was done using biochemical testing. From 2019 onwards, 16s rRNA based-DNA sequencing was implemented for speciation (outside study period).



Figs 1A and B: Composite image with Gram's staining of sputum sample. (A) Branching of gram-positive thin filamentous organisms consistent with *Nocardia* spp; (B) Modified acid-fast staining confirmed that these organisms were acid-fast

Treatment Protocol for PN

All admitted patients received meropenem 1 g every 8 hours for 2–4 weeks, along with oral or parenteral cotrimoxazole (15 mg/kg trimethoprim equivalent in three divided doses); cotrimoxazole alone was then continued for the remaining duration of 6 months. All patients with PN were admitted only till clinical stabilization as defined by absence of fever, normal hemodynamics and need for minimal or no oxygen; parenteral antibiotics were continued on ambulatory basis or arranged at a center of convenience for the prescribed period. In mild PN treated as outpatient basis, cotrimoxazole alone (10 mg/kg trimethoprim equivalent in three divided doses) was administered. In cases of suspected or proven disseminated nocardiosis, amikacin 15 mg/kg was added for the initial period and the initial intensive phase was extended from four to 6 weeks.[10,11]

Data Extraction

Data was abstracted in a predefined data extraction form. From the selected cases, the following data were gathered: (a) demographic details of each case including age and gender, (b) duration of symptoms, (c) symptoms at presentation, (d) type of chronic lung disease, (e) body mass index, (f) co-morbidities and their details, including smoking, alcohol abuse, diabetes, chronic kidney disease, steroid receipt in the last 6 months before diagnosis and concurrent malignancy, (g) diagnosis of chronic respiratory failure before the diagnosis of PN, (h) spirometry values, (i) laboratory investigations, including total leukocyte counts, arterial blood gas analysis, (j) radiologic findings and echocardiography, (k) microbiologic isolates, (l) treatment administered, including details of steroids, antimicrobial therapy and their duration, oxygen use, noninvasive or invasive ventilation and its duration, and (m) outcomes; discharge on domiciliary oxygen and hospital mortality.

Outcome Measures

The duration of symptoms prior to presentation, symptoms, laboratory findings, radiologic findings, treatment administered and outcomes were compared between patients with AE-CPD_b and AE-CPD_{PN}

Statistics

Statistical analyses were performed using SPSS version 14. Continuous variables were described in a descriptive fashion (mean ± SD, median, IQR) and discrete variables were described as frequency proportions. Comparisons for continuous variables were performed using the independent T test or Mann–Whitney test and proportions using the Chi-square test or Fisher's exact test, where appropriate. Statistical significance was assessed at the 2-sided $p \leq 0.05$ level. The independent association of AE-CPD_{PN} with the need for noninvasive or invasive mechanical ventilation and mortality was tested by logistic regression.

Ethics

The Research Ethics Committee of our Hospital approved this study. All data abstracted was anonymized, thus ensuring confidentiality and patient privacy.

Results

There were a total of 32 cases of PN over a 10-year period. We excluded 10 cases, including five with disseminated nocardiosis without coexisting CPD. There were a total of 22 cases of AE-CPD_{PN}, including 13 men and 9 women; all had localized pulmonary disease. The type of CPD was most commonly bronchiectasis (59%, 13/22), followed by COPD (36.4%, 8/22) and ILD (1/22, 4.5%) (Table 1A). Bronchiectasis was cystic (CB) and multilobar in all and the etiology was idiopathic, post-tuberculosis or allergic bronchopulmonary aspergillosis (ABPA)-related. 21/22 of AE-CPD_{PN} had inhaled corticosteroids (ICS) use compared to 63/66 of the controls; these were patients with advanced airway disease and were on triple therapy and ICS use was not different in cases compared to controls. The final 22 AE-CPD_{PN} included did not have any oral steroid intake in the 12 months prior to the diagnosis of PN. The patient with AE-CPD_{PN} related to ILD was steroid-naïve and the diagnosis of ILD was made concurrent with the diagnosis of PN. Two patients with AE-CPD_{PN} received steroids for severe bronchospasm with a diagnosis of AE-CPD_b before the diagnosis of PN; in both, steroids were discontinued after diagnosis. Among patients with AE-CPD_b, *Pseudomonas aeruginosa* was the most common organism isolated. 27.2% (6/22) of the patients with AE-CPD_{PN} had a presumed or proven bacterial coinfection. All patients with AE-CPD_{PN} were treated with cotrimoxazole for a median (IQR) duration of 6(2) months. Two patients were subsequently treated with other regimens after discontinuation of cotrimoxazole; reasons included inability to tolerate cotrimoxazole due to persistent severe hyperkalemia and in another, the isolate was reported as *N. farcinica* resistant to cotrimoxazole in association with clinical failure.

Table 1A: Comparison between patients with exacerbations of chronic lung disease due to Nocardia and bacterial exacerbations of chronic lung disease

Characteristics	*Nocardia related exacerbation (n = 22)*	*Bacterial exacerbations (n = 66)*	*P value, **OR 95% CI*
Age years, mean ± SE	61.36 ± 2.9	60.5 ± 1.7	0.79
Gender, male: female	13:9	39:27	1.00
Etiology of chronic lung disease before diagnosis	COPD (8/22), BXSIS (13/22), ILD (1/22)	COPD (24/66), Bronchiectasis (39/66), ILD (3/66)	1.00
Body mass Index kg/m^2 mean ± SE	18.6 ± 1.2	21.3 ± 0.9	0.08
Risk factors			
	Smoking (8/22, 36.4%), alcohol abuse (3/22, 13.6%)	Smoking (28/66, 42.4%), alcohol abuse (8/66, 12.1%)	N.S
	*Recent steroid intake (2/22, 9.1%)	Recent steroid intake (6/66, 9.1%)	1.00
	Diabetes (6/22, 27.2%)	Diabetes (16/66, 24.2%)	N.S
	Prior tuberculosis (9/22, 40.9%)	Prior tuberculosis (14/66, 21.2%)	0.08
Symptoms at presentation			
Fever	10/22 (45.4%)	19/66 (43.9%)	0.07
Cough	20/22 (90.9%)	60/66 (90.9%)	0.83
Dyspnea	16/22 (72.7%)	61/66 (92.4%)	OR 0.17 (0.04–0.69), $p = 0.01$
Chronic respiratory failure before diagnosis	0/22 (0%)	28/66 (42.4%)	OR 0.03 (0.0–0.51), $p < 0.001$
Duration before presentation, days (Median, IQR)	12, (23)	7, (8)	0.001
Spirometry			
FEV/FVC%, mean ± SE	68 ± 7.23	63.2 ± 4.95	0.65
FEV1 L, % mean ± SE	1.01 ± 0.05L, 53.6 ± 2.4%	1.1 ± 0.1 L, 45.4 ± 4.9%	0.71
FVC L, % mean ± SE	1.5 ± 0.1 L, 58.0 ± 2.1%	1.7 ± 0.2 L, 54.4 ± 5.8%	0.55
Total leukocyte count/µL, Mean ± SE	17985 ± 228/µL	12426 ± 65/µL	0.002
N%, Absolute neutrophil count/µL, mean ± SE	83.6 ± 2.8%, 14420 ± 238/µL	78.6 ± 1.4%, 10027 ± 63/µL	0.01
Hemoglobin g/dL, mean ± SE	11.8 ± 0.4	12.4 ± 0.2	0.24
Erythrocyte sedimentation rate mm/hr, mean ± SE	62.2 ± 5.9	37.1 ± 3.3	<0.001
Renal failure at diagnosis	2/22 (9.1%)	22/66 (33.3%)	OR 0.2 (0.04–0.9), $p = 0.02$
Arterial blood gas at diagnosis			
pH, mean ± SE	7.43 ± 0.01	7.36 ± 0.01	0.016
paO_2 mm Hg, mean ± SE	73.2 ± 5.3	88.8 ± 4.9	0.14
$paCO_2$ mm Hg, mean ± SE	38.9 ± 3.3	51.6 ± 2.2	0.013
HCO_3 mEq/L, mean ± SE	25.0 ± 1.5	28.3 ± 0.8	0.06

There was no difference in body-mass index, lung function at baseline, presence of obstruction on spirometry, presence of risk factors like smoking, alcohol abuse, recent steroid intake, diabetes or prior tuberculosis between AE-CPD_b, and AE-CPD_{PN} (Table 1B). When compared to age, gender and type of CPD-matched AE-CPD_b, AE-CPD_{PN} had longer symptom duration (median difference 5 days, $p = 0.014$) prior to presentation. There was more leukocytosis (mean difference 5559/µL, $p = 0.002$), neutrophilia (mean difference 4373/µL, $p = 0.01$) and higher erythrocyte sedimentation rate (mean difference 25.1 mm/hour, $p < 0.001$) at hospitalization. Patients with AE-CPD_b had higher proportion with dyspnea at presentation (OR 4.57, $p = 0.02$), chronic respiratory failure prior to diagnosis of bacterial exacerbation (OR 33.3, $p = 0.01$), and more respiratory acidosis (pH difference –0.04, $p = 0.016$, $PaCO_2$ difference 12.7 mm Hg, $p = 0.01$) at diagnosis. More patients with AE-CPD_b had acute kidney injury (AKI, O.R 5.0, 95% CI 1.07–23.3, $p = 0.04$) at diagnosis, with 22.7% (5/22) requiring dialysis. Two patients with AE-CPD_{PN} had renal failure, with both requiring dialysis. There was also higher proportion of left ventricular systolic or diastolic dysfunction (OR 5.27, 95% CI 1.34-20.7, $p = 0.01$) and pulmonary hypertension (OR 6.2, $p = 0.008$) in patients with AE-CPD_b.

On imaging, AE-CPD_{PN} had higher proportion of consolidation (95.5%) and cavitation (27.3%). Consolidation was mass-like, multilobar or multifocal in all patients with AE-CPD_{PN}. (Figs 2 and 3). On univariate analysis, there was no difference in the need for oxygen, noninvasive ventilation or mechanical ventilation between

Table 1B: Comparison of findings and clinical course between patients with exacerbations of chronic lung disease due to Nocardia and bacterial exacerbations of chronic lung disease

Characteristics	*Nocardia related exacerbation*	*Bacterial exacerbations*	*P value, OR 95% CI*
Arterial blood gas at presentation	Hypoxemia (69.2%), type 1 (23.1%), type 2 failure (7.7%)	Hypoxemia (28.6%), type 1 (16.1%), type 2 failure (55.4%)	**OR 0.05, (0.007–0.44), $p = 0.006$
Radiological findings at diagnosis			
Consolidation	21/22 (95.5%)	53/66 (80.3%)	0.06
Cavitation	6/22 (27.3%)	4/66 (6.1%)	5.81 (1.46–23.1), $p = 0.01$
Pleural effusion	2/22 (9.1%)	2/66 (3%)	0.26
Cardiac findings			
Cardiac disease	LVSD (0/17), LVDD (3/17, 17.6%)	LVSD (5/49, 10.2%), LVDD (21/49, 42.8%)	OR 0.18 (0.04–0.74), $p = 0.01$
Pulmonary hypertension	3/17 (17.6%)	28/49 (57.1%)	OR 0.16 (0.04–0.63), $p = 0.008$
Microbiological evaluation			
Etiology of exacerbations	*Nocardia* (22/22, 100%), bacterial coinfections (6/22, 27.2%)	No growth (49/66, 74.3%), *Pseudomonas* 9/66 (13.6%), others (6/66, 9.1%)	NA
Treatment details			
New respiratory failure needing oxygen	9/22 (40.9%)	21/66 (33%)	O.R 1.48, $p = 0.44$
Oxygen duration days, median, IQR	5 (10.75)	5 (3)	0.50
NIPPV	5/22 (22.7%)	23/66 (34.8%)	0.28
NIPPV duration days, median, IQR	4 (7)	6 (2.5)	0.29
Mechanical ventilation	5/22 (22.7%)	6/66 (9.1%)	O.R 2.94 (0.79–10.8), $p = 0.10$
Mechanical ventilation duration days, median, IQR	2 (5.75)	3.5 (1.75)	0.32
Hospital length of stay days, Median, IQR	8 (9)	5 (4)	0.016
Antibiotic receipt	Cotrimoxazole (20/22), minocycline (1/22), others (1/22)	Penicillins (29/66, 43.9%), Cephalosporins (25/66, 37.8%), FQ (8/66, 12.1%)	NA
Duration of cotrimoxazole months median, IQR	6 (2)	NA	NA
Steroids during exacerbation	2/22 (9.1%)	26/66 (39.4%)	OR 0.15 (0.03–0.71), $p = 0.01$
Discharged on home oxygen	3/17 (17.6%)	35/66 (53%)	OR 0.18 (0.04–0.72), $p = 0.01$
Alive at hospital discharge	17/22 (77.3%)	66/66 (100%)	OR 41.8 (2.2–792.7), $p = 0.01$

**Odds ratios are presented for significant associations

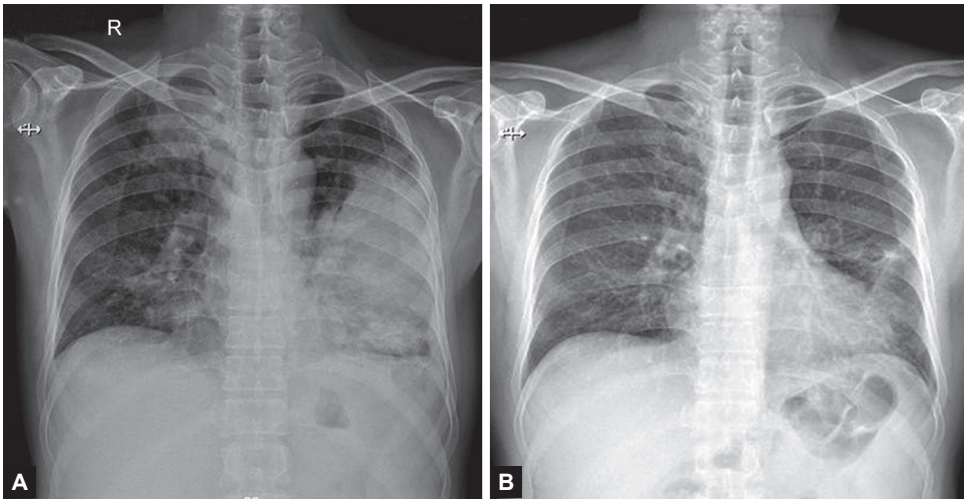
N%, percentage of neutrophils; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; pH, inverse log of proton concentration; PaO_2, partial pressure of oxygen; $PaCO_2$, partial pressure of carbon dioxide; HCO_3, serum bicarbonate; LVSD, left ventricular systolic dysfunction; LVDD, left ventricular diastolic dysfunction; ASD, atrial septal defect; PH, pulmonary hypertension; *≤3 months from diagnosis; NIPPV, noninvasive positive pressure ventilation; FQ, fluoroquinolone; SD, standard deviation; IQR, interquartile range; OR, odds ratio; CI, confidence interval

AE-CPD_{PN} and AE-CPD_b. Patients with AE-CPD_{PN} had a longer stay for clinical stabilization ($p = 0.016$) and more patients with AE-CPD_b were discharged on domiciliary oxygen (O.R 5.27, $p = 0.01$). On multiple logistic regression, after adjusting for higher illness severity of AE-CPD_b, AE-CPD_{PN} was independently related to need for mechanical ventilation (OR 22.3, $p = 0.01$), length of hospital stay (median difference, 4 days, $p = 0.016$) but not to hospital mortality (Table 2).

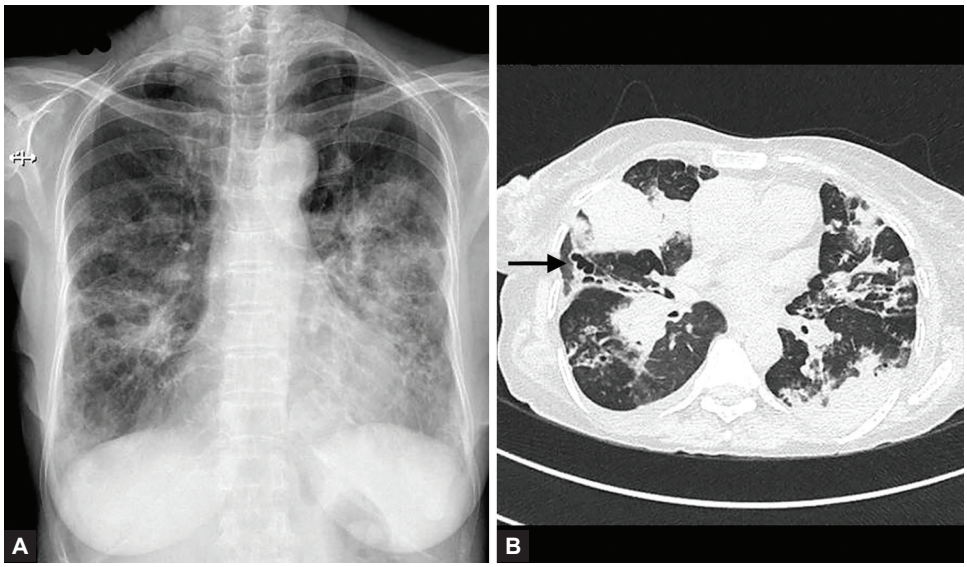
AE-CPD_{PN} was associated with a 22.7% (5/22) mortality. There was no difference in recent receipt of steroids prior to diagnosis of PN, renal failure at diagnosis, pH or hospital stay between survivors and nonsurvivors (Table 3). Respiratory failure requiring oxygen, NIPPV or mechanical ventilation was associated with mortality in AE-CPD_{PN}.

Discussion

Pulmonary nocardiosis is a rare thoracic infection predominantly affecting immunocompromised hosts.[8] The traditional risk factors for PN include long-term steroid therapy, malignancy, chemotherapy and HIV infection.[11] However, one-third of cases reportedly occur in immunocompetent patients.[12] There is increasing recognition that COPD is a risk factor for PN.[13] Data are mostly from case reports and small series, given the rarity of PN.[3,4,14-16] Notably, several of these cases have COPD associated with bronchiectasis and this is an important but under-recognized risk-factor for PN as well.[3,13] In our series, bronchiectasis was the most common underlying CPD. No clustering of cases was noted and only five of the 22 cases were diagnosed and managed in the outpatient non-CF bronchiectasis



Figs 2A and B: Composite image with chest radiograph (A) of a patient with pulmonary nocardiosis-related chronic pulmonary disease exacerbation showing multilobar consolidation, with a dense mass-like consolidation in the left lingula. Bronchoscopic biopsy from lingula confirmed nocardiosis; (B) Repeat chest radiographs at 6 months of cotrimoxazole showed resolution with a small area of residual fibrosis



Figs 3A and B: (A) Composite image with chest radiograph of a patient with pulmonary nocardiosis-related chronic pulmonary disease exacerbation showing multilobar consolidation; (B) Computed tomography confirmed extensive consolidation and also showed bronchiectasis (thin arrow)

Table 2A: Univariate logistic regression of the association of *Nocardia*-related exacerbations and need for mechanical ventilation

	Nocardia-related versus bacterial exacerbation			
	Odds ratio	*Lower*	*Upper*	*p value*
Renal failure	0.2	0.043	0.93	0.041
Respiratory failure	0.18	0.051	0.64	0.008
pH (unit change = 0.1)	3.99	1.424	15.18	0.02

Table 2B: Multiple logistic regression of the association of *Nocardia*-related exacerbations and need for mechanical ventilation (*after adjusting for renal failure and respiratory failure before diagnosis)

	Nocardia-related vs bacterial exacerbation			
	Odds ratio	*Lower*	*Upper*	*p value*
Need for mechanical ventilation	22.34	2.04	282.3	0.01*

clinic. None of the cases with AE-CPD$_{PN}$ had received long-term steroids before diagnosis, including all the patients with ABPA. In one-third of the cohort, the diagnosis of CPD was made when they presented with AE-CPD.

Thoracic involvement is the most common presentation of PN and is seen in 85% of cases at presentation. Symptoms are nonspecific and this is especially true with PN presenting in patients with CPD.[4,8] PN in CPD presents with an exacerbation of the underlying respiratory symptoms and is often similar to bacterial exacerbations of CPD (AE-CPD$_b$).[17] In fact, two cases of PN in our series were initially diagnosed as AE-CPD$_b$ and improved with antibacterials for AE-CPD; early relapse of symptoms after discontinuation of antibiotics for AE-CPD$_b$ (typically seven days in our practice) prompted extensive microbiological evaluation, yielding a diagnosis of AE-CPD$_{PN}$. This study was conducted in this background to identify clinical features that can distinguish AE-CPD$_{PN}$ from AE-CPD$_b$.

Table 3: Comparison of clinical features of AE-CPDPN between survivors and nonsurvivors

Characteristic	*Survivors (n = 17)*	*Nonsurvivors (n = 5)*	*Statistics*
Age years, mean ± S.D	60.5 ± 14.9	64.0 ± 10.7	0.64
Gender males: Total	9/17 (52.9%)	4/5 (80%)	0.36
Body mass index, Kg/m^2, mean±S.D	18.2 ± 5.2	21.4 ± 3.4	0.58
Duration before presentation, days median, range	12 (88)	8 (116)	0.57
Recent steroids (<3 months) before diagnosis	2/17 (11.8%)	0/5 (0%)	1.00
Hemoglobin g/dL	11.5 ± 2.2	12.8 ± 1.2	0.27
Total leukocyte count//µL, Mean ± S.E	16462 ± 2422	22860 ± 5630	0.34
pH, Mean ± S.D	7.44 ± 0.06	7.40 ± 0.05	0.16
paO_2 at diagnosis, Mean ± S.D	73.2 ± 18.3	73.2 ± 22.6	1.00
Chronic respiratory failure before diagnosis	0/17	0/5	NA
Renal failure at diagnosis	1/17 (5.9%)	1/5 (20%)	0.41
Cavity on chest imaging	4/17 (23.6%)	2/5 (40%)	0.58
Nocardia vs coinfection	5/17 (29.5%)	1/5 (20%)	1.00
Respiratory failure needing oxygen	4/17 (23.6%)	5/5/ (100%)	0.005
NIPPV	2/17 (11.8%)	3/5 (60%)	0.05
Mechanical ventilation	2/17 (11.8%)	3/5 (60%)	0.05
Hospital length of stay days Median, IQR	10 (9)	5 (13)	0.25

SD, standard deviation; IQR, interquartile range

We did not find additional risk-factors independent of CPD predisposing to PN in our series (Tables 1A and 1B), again establishing the independent risk of CPD for PN.[13] AE-CPD_{PN} occurred in patients with advanced lung disease (mean FEV1 1.01 ± 0.05 L, 53.6 ± 2.4% predicted) who presented with longer symptom duration, more leukocytosis and inflammatory markers when compared to AE-CPD_b. Extensive consolidation or cavitation prompted suspicion for PN in AE-CPD and cavitation was seen in 27.3% at diagnosis. Four patients with AE-CPD_b had an initial diagnosis of cavitation; one was related to an exacerbation of COPD related to previous tuberculosis and in another three, underlying bronchiectasis had not been diagnosed and consolidation around cystic bronchiectasis spaces was initially misdiagnosed as cavitation.

The cohort of AE-CPD_b was sicker with a higher proportion of cardiac disease, pulmonary hypertension, chronic respiratory failure on long-term oxygen therapy, respiratory acidosis and AKI at presentation. Consequently, more patients with AE-CPD_b were treated with oxygen, NIPPV (though statistically non-significant) and were discharged on domiciliary oxygen. After adjustment for the higher illness severity of AE-CPD_b, AE-CPD_{PN} was independently related to the need for mechanical ventilation and duration of hospital stay. The in-hospital mortality of 22.7% in AE-CPD_{PN} is similar to previous published reports of PN.[4] Respiratory failure requiring oxygen therapy, NIPPV or mechanical ventilation was associated with mortality in AE-CPD_{PN}.

Our study has several strengths. This is one of the largest series of PN in immunocompetent CPD till date. In another large series of 30 patients with PN-CPD, 23% (7/30) were related to chronic steroid therapy, chemotherapy and malignancy. Associated immune-compromise was associated with mortality and this masked the mortality associations of PN-CPD *per se*.[4] We also identified a matched cohort of AE-CPD_b to identify clinical features that could help in early diagnosis of PN in AE-CPD. There are several limitations of this study. The retrospective nature of the study resulted in an imbalance in the baseline characteristics between cases and controls; controls had more preexisting respiratory failure than cases. PN is a rare disease and conducting prospective studies is not always feasible. Second, we included patients with consolidation in the control group of AE-CPD_b. While this is debatable,[1,18] we aimed at a control group with similar severity of illness to AE-CPD_{PN} and including AE-CPD_b with consolidation was considered appropriate as most patients with AE-CPD_{PN} had consolidation at diagnosis. While some reports of AE-CPD exclude those with consolidation, this would have prevented us from identifying clinical features that help in early diagnosis of AE-CPD_{PN}. Third, data on speciation of *Nocardia* spp. is being revised with 16sRNA studies and our data is currently not available. It is well described that extensive discrepancy between biochemical testing and 16sRNA testing occurs and leads to re-speciation.[19] Fourth, most of the cases of PN (22/32, 68.75%) in the current series were related to CPD; this is possibly because of high index of suspicion in our unit and the absence of hemato-oncology and organ transplant specialty service till 2016 in our hospital. Finally, the absence of spirometry reports for the five patients who died may have lead to over-estimation of values in the AE-CPD_{PN} arm. As has been described, 29% were diagnosed with CPD when they presented with AE-CPD and it was not always feasible to do spirometry.

Conclusion

In conclusion, PN is a rare cause of AE-CPD and can be recognized by a longer symptom duration, leukocytosis, extensive consolidation and cavitation. Early recognition is important, given the high short-term mortality. AE-CPD_{PN} is independently associated with longer duration of hospital stay and mechanical ventilation. Respiratory failure requiring oxygen, NIPPV and mechanical ventilation is associated with mortality in AE-CPD_{PN}.

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