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An Observational Study on Etiology of Non-Resolving Pneumonia in a Tertiary Care Hospital of Karachi, Pakistan

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A B S T R A C T

Background: Non-resolving pneumonia (NRP) is a disease process of lung parenchyma that lacks significant symptomatic improvement and/or has less than 50% resolution by 2 weeks or incomplete resolution by 4 weeks despite appropriate antimicrobial therapy (generally considered to be of 10-14 days duration). Studies suggest that NRP may account for 10-15% of nosocomial pneumonias, 15% of inpatient pulmonary consultations, and 8% of bronchoscopies done in a tertiary care setting.

Objective: The present study was conducted with the objective of the study was to delineate the various causes of NRP as well as its association with patient characteristics, radiographic characteristics, and clinical outcomes.

Methodology: This was a descriptive retrospective observational study. Data was collected over from September 2019 to January 2021. Overall, 29 outpatient files coded as NRP and 237 inpatient files labeled as pneumonia were reviewed. Of these, 33 patients met the eligibility criteria and were systematically assessed with regards to study objective.

Results: Average age at NRP diagnosis was 55.15±18 years. Smoking was a significant comorbidity in 48% of patients. Regarding radiographic imaging, no associations were observed. Sputum cultures demonstrated 33% positivity, whereas lung biopsy successfully identified the underlying etiology in all those who underwent this procedure. Tuberculosis (40.1%), malignancy (21.2%) and Aspergillus lung disease (18%) were the most common causes of NRP. Excluding those who lost to follow up and died, every patient had complete symptomatic recovery and 96% radiographic resolution within 6 months of initiation of treatment was noted.

Conclusion: This study stresses that biopsy serve as the gold standard for NRP diagnosis. Moreover, although the diagnosis of NRP may be a challenge, treatment is certainly possible.

Keywords: Non-resolving pneumonia; Etiology; Tuberculosis; Aspergillus; Lung biopsy

Introduction

Non-resolving pneumonia (NRP) is a disease process of lung parenchyma that lacks significant symptomatic improvement and/or has less than 50% resolution by 2 weeks or incomplete resolution by 4 weeks despite appropriate antimicrobial therapy (generally considered to be of 10-14 days duration).1,2 Studies suggest that NRP may account for 10-15% of nosocomial pneum-onias, 15% of inpatient pulmonary consultations, and 8% of bronchoscopies done in a tertiary care setting.3,4

NRP may have an infectious or a non-infectious origin. An interplay of host and environmental factors such as age and immune status, the presence of resistant/unusual organisms, as well as the extent co-morbid conditions can all amalgamate and lead to NRP. Host factors such as smoking, history of malignancy and its treatment, inflammatory disorders, and drug toxicities increase the chances of developing NRP.5,6

Evaluation of NRP may necessitate cultures and other diagnostic measures such as bronchoalveolar lavage and/or lung biopsy. Imaging studies such as chest x-ray and chest CT are also important for the diagnosis and management of NRP. These investigations may carry a significant financial burden, especially in lower middle-income countries (LMICs) and areas with poor public healthcare systems such as Pakistan. Currently, there are no studies assessing the etiologies of NRP in our country. The present study aimed to delineate the various causes of NRP, as well as its association with patient characteristics, radiographic characteristics, and clinical outcomes.

Objective

The present study was conducted with the objective of the study was to delineate the various causes of NRP as well as its association with patient characteristics, radiographic characteristics, and clinical outcomes.

Methodology

This was a descriptive retrospective observational study conducted at Aga Khan University Hospital (AKUH), a tertiary care teaching center over the period of September 2019 to January 2021. The study protocol was approved by the Ethical Review Committee (ERC) of AKUH. Data was anonymized using Unique Identity Numbers (UIN) and was only accessible to members of the research team. The study's inclusion criteria encompassed adult patients aged over 18 exhibiting clinical signs and symptoms indicative of pneumonia, including fever, cough, dyspnea, and chest pain. Additionally, patients must have displayed delayed or non-resolution of lung infiltrates on chest imaging despite receiving appropriate antimicrobial therapy, with less than 50% resolution within two weeks or incomplete clearance by four weeks. Conversely, exclusion criteria comprised patients lacking either clinical or radiological records and those lost to follow-up prior to establishing a conclusive diagnosis of non-resolving pneumonia (NRP). Patient data including host factors, symptoms, comorbidities, treatment history, and investigation results were collected with the use of a structured questionnaire. Data entry and analysis was performed using Statistical Package for Social Sciences (SPSS) version 24.0.

Results

The mean age of our cohort was 55.15±18 years. Of 33 patients, 17 were male (51.5%) and 16 were female (49.5%). There was an almost equal number of patients with and without smoking history, and few patients had a history of alcohol intake. The most common comorbidities were hypertension (n=10, 30.3%) and obstructive airway disease (n=7, 21.2%). Eleven (33.3%) patients had a history of pneumonia in the past six months, and thirteen (39.4%) patients had used antibiotics for greater than two weeks prior to initial care (Table 1).

The site of initial care was inpatient for fifteen (45.5%) patients and outpatient for eighteen (54.5%) patients. Fifteen (45.5%) of the patients had a presenting illness of less than 30 days, while the rest presented with symptoms for more than a month. The most common presenting symptoms were cough (n = 30, 93.8%), fever (n = 25, 75.8%), dyspnea (n = 23, 69.7%), and fatigue (n = 19, 57.6%). Thirteen (39.3%) patients also presented with weight loss and eleven (33.3%) had chest pain.

All patients underwent radiological imaging with chest x-ray, and 27 received additional imaging with chest computed tomography (CT). There was similar distribution regarding unilateral (n = 17, 53.1%) and bilateral (n = 15, 46.9%) lung involvement. Consolidation was the most frequent abnormality (n = 30, 93.8%), followed by lymphadenopathy (n = 16, 48.5%). In terms of infiltrates, nodular infiltration (n = 12, 36.4%) was more common than interstitial (n = 4, 6.3%). Additionally, five (15.6%) patients exhibited cavitary lesions and seven (21.2%) showed pleural effusion.

In terms of diagnostic investigations, every patient underwent either a sputum culture (n=30, 90.9%) and/or a bronchoalveolar lavage (n = 13, 36.4%). Of the patients that underwent a sputum culture, 11 (33.3%) yielded positivity. Seven patients returned positive cultures for tuberculosis (TB), 1 for nocardia, and 3 for aspergillosis. Four (12.1%) patients underwent thoracentesis, and one patient's culture yielded positivity. There were 18 (54.5%) patients that underwent lung biopsy. Eight patients each underwent either a CT-guided or transbronchial route for

Table 1. Demographic Characteristics of Study Patients

Descriptive Statistics	Frequency (%)
Age (Mean ± SD), Years	55.15±18
Gender	
Male	17 (51.5)
Female	16 (48.5)
History of smoking	
Current Smoker	4 (12.2)
Ex-Smoker	12 (36.3)
Non-Smoker	17 (51.5)
History of alcohol intake	2 (6.1)
Comorbidities	
Obstructive Airway Disease	8 (24.2)
Pulmonary Fibrosis	1 (3)
Coronary Artery Disease	5 (15.2)
Hypertension	10 (30.3)
Chronic Kidney Disease	1 (3)
Obesity	3 (9.1)
Multiple Myeloma	1 (3)

SD = Standard Deviation

lung biopsy, and 1 patient each via ultrasound guided and surgical route. All biopsy results yielded positive histopathology.

In our study, pulmonary TB (39.4%) was found to be the most common etiology of NRP. This was followed by aspergillus lung infection (18.2%), and adenocarcinoma of the lung (9%). Other etiologies of NRP are listed in Table 2.

There were twenty three patients in the cohort that had radiological resolution within 6 months. One (5%) patient had radiological resolution within 1 month of treatment, three (14%) patients had radiological resolution within 2 months, and a majority (n=19, 79.2%) achieved radiological resolution within 3-6 months.

Of the patients included in the study, majority achieved full symptomatic recovery (n=24, 72.3%). There was one death in the cohort due to hypoxic respiratory failure (3%), and eight (18.2%) patients were lost to follow up.

Discussion

NRP has had varying definitions over the years, with a lack of uniformity regarding its classification.1,2 Our study defined NRP by merging the definitions of Kyprianou *et al.* and Kirtland *et al.* as this provides quantitative criterion for the minimal duration of treatment deemed adequate as well as delayed radiographic resolution.1,2 This conjoined definition has been used previously in studies assessing

the etiologies of NRP.7

NRP can be a diagnostic dilemma and patients are usually subjected to multiple investigations. Pakistan is a LMIC with a poor public health infrastructure. Given these circumstances, knowledge regarding NRP may prove invaluable to treating physicians in the region and in other countries with poor public health facilities.

Many risk factors are implicated with non-resolution of pneumonia. Advancing age has been shown to cause impaired immunity and decreased lung function.8 This increases the likelihood of delayed resolution of pneumonia, and thus can contribute to NRP. Our study population had an average age of 55, with 79% of the cohort over the age of 40 and 52% over the age of 60. This was in accordance with previous studies that also found most NRP patients are over the age of 40.9,10 Another factor linked with NRP is the male gender. Previous studies indicate that NRP predominantly affected males.9,11 This was not the case in our study, as NRP exhibited similar gender distribution. Other patient characteristics seen in our study, such as a history of smoking (48.5%), obstructive airway disease (24.2%) pulmonary fibrosis (3%), chronic kidney disease (3%), and the use of immunosuppressants (15.2%) are well established factors that increase the likelihood of pneumonia and delay its resolution.12 Other factors such as HIV, asplenia, and alcoholism are also associated with a delayed resolution of pneumonia but were not present in our cohort.12 On the other hand, hypertension (30.3%) and coronary artery disease (15.2%) were also common comorbidities seen in our patient population. However, no association exists between these cardiovascular diseases and the progression of pneumonia.13 King *et al.* demonstrated that obesity (seen in 9.1% of our patients) has no impact on the clinical outcomes of pneumonia when stratified for confounders.14

Radiographic indices facilitate physicians in elucidating underlying pathologies as well as in monitoring disease progression. Our cohort disclosed a similar distribution of unilateral and bilateral lung involvement, contrasting similar NRP studies in which unilateral lung involvement predominated.9,10 Consolidation was the most preva-

Table 2. Diagnosis of Non-resolving Pneumonia

Variables	Frequency (%)
Infectious Origin	
Mycobacterium Tuberculosis	13 (65%)
Aspergillus	6 (30%)
Nocardia	1 (5%)
Malignant Etiology	
Adenocarcinoma of the Lung	3 (42.9%)
Small Cell Lung Carcinoma	1 (14.3%)
Hodgkin's Lymphoma	2 (28.6%)
Diffuse Large B Cell Lymphoma	1 (14.3%)
Other Etiology	
Cryptogenic Organizing Pneumonia	2 (40%)
Chronic Eosinophilic Pneumonia	1 (20%)
Anthracosis	1 (20%)
Granulomatosis with Polyangiitis	1 (20%)

lent lung feature in our cohort, and this finding mirrored other papers assessing NRP.9,10 As consolidation can be secondary to an assortment of pulmonic insults, it holds little value in discerning an underlying etiology. Similarly, nodular infiltrates, found in more than a third of our cohort, are also a non-specific finding that may represent various pathological entities that can cause NRP, including TB, aspergillus, and malignancies. Notably, there were five patients that exhibited cavitation in the lung fields, two of which were eventually diagnosed with TB. TB associated with lung cavities was a prominent cause of NRP in multiple studies. These studies also found most NRP secondary to TB illustrate bilateral lung involvement.9,10 In comparison, only 38% of our cohort diagnosed with TB showed similar lung distribution. Other indices we delineated such as interstitial infiltrates, lymphadenopathy, and pleural effusion were integral in the monitoring of disease resolution. In general, our study did not show significant predilection of any pathology with a lung region.

For diagnosis, sputum cultures were obtained from most patients, of which a third yielded positivity. Eighteen patients underwent a bronchoscopic biopsy of lung tissue, with different approaches utilized based off individual characteristics. Previously, Feinsilver et al. found fiberoptic biopsy had close to a 90% specificity for determining NRP etiology,15 and Chaudhuri et al. demonstrated successful diagnosis in 86% of patients presenting with NRP in his study.10 All 18 patients that underwent a biopsy in our study demonstrated etiology findings. This suggests that bronchoscopic lung biopsy should be the gold standard for diagnosis of NRP.

The most common cause of NRP in our study was pulmonary TB (40.1%). Given the geographic location and regional similarities between Pakistan and India, this finding is in parallel with that seen in the patients of Tummuru et al. (39.28%) and Jayprakash et al. (25.7%).7,9 These patients were prescribed six months of anti-tuberculous medications and 11 patients showed radiographic resolution within 6 months. Two of these patients were lost to follow-up, thus it was not possible to assess their treatment adherence and radiologic lung status. Although the gold standard for diagnosis of pulmonary TB is sputum culture, only 7 patients in our cohort yielded positive cultures, accounting for only 54% of the TB cases in our study. Given its high prevalence in the region, one must consider underlying tuberculous as a likely cause of NRP, even in the absence of typical symptoms in our setting.

Aspergillus was the second most common cause of NRP (18%). It is the most prevalent environmental fungus found both indoors and outdoors, and previous studies have revealed the high burden of chronic aspergillus pneumonia in our country.16,17 Aspergillus has been associated with obstructive airway disease and TB;18 however, this association was not identified in our cohort.

There were seven (21.2%) cases of malignancy of NRP in our cohort. Our data did not suggest correlation with smoking status and malignant NRP compared to other study,9 as three of these patients were ex-smokers and four had never smoked. Bronchoscopic biopsy provided the definitive diagnosis, further highlighting its value in NRP. Three of these patients were diagnosed with lung adenocarcinoma (ADC). ADC is the most common lung neoplasm by histology, and a new sub-classification of ADC is pneumonic-type lung adenocarcinoma (P-ADC).19 P-ADC is described as an adenocarcinoma with pneumonia-like infiltrates or consolidation.20 Given its radiographic similarity with pneumonia, it may be lower in the differentials of NRP in many patients, especially those without typical risk factors. All three patients with ADC in our cohort had multilobed involvement, consolidation, and surrounding nodular infiltrates. These triad of imaging findings are suggested in previous studies to indicate the P-ADC rather than pneumonia.21 Additionally, two patients were diagnosed with Hodgkin's lymphoma and one patient with DLBCL on histopathology. These malignancies rarely present as primary lung pathologies, but both commonly have secondary pulmonary involvement. The malignancies identified in our study differed from those seen in other studies, which primarily found bronchogenic carcinoma and squamous cell carcinoma as NRP cases.7,9,10

Other etiologies of NRP identified in our study included two patients with cryptogenic organizing pneumonia (COP). COP can develop secondary to a multiple of systemic illnesses and medications. It is typically associated with a viral-like prodrome and is characterized by bilateral lung consolidation with interstitial infiltrates.23 Diagnosis can be confirmed by bronchoscopy, and treatment included corticosteroids, which often shows symptom improvement within 3-4 days and radiographic normalization within 1-4 weeks.23 It is also worth highlighting that one patient in our cohort was diagnosed with granulomatosis with polyangiitis (GPA). Many studies have identified this as a rare cause of NRP, and this condition carries up to 80% mortality in those left untreated.'24,25 Vasculitides such as GPA should be strongly considered in those with a history of concomitant otolaryngologic, renal, or other extrapulmonary disease.

There were several limitations in our study. This was a single center retrospective study, and given the small sample size of our cohort, our study was underpowered to establish associations between patient characteristics, radiographic findings, and specific etiologies of NRP. More multicenter studies throughout the country are recommended to further understand this challenging disease.

Conclusion

In conclusion, our study suggests that infections and malignancy were the commonest diagnoses of NRP. A thorough evaluation is needed to rule out malignant cause. This study emphasizes that biopsy serves as the gold standard for NRP diagnosis.

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