NON-RESOLVING PNEUMONIA AETIOLOGY AND CLINICAL PROFILE: A PROSPECTIVE STUDY

Binuraj Chathamparamb[1], Anil Antony[2], Sruti Ullas Nivarthil[3], Ann Mary Paul[4], Mrudhul Asok Kallikadavil[5], Manas Joshi[6]

[1]Associate Professor, Department of Pulmonary Medicine, KMCT Medical College, Calicut.
[2]PharmD, Department of Pharmacy Practice, National College of Pharmacy, Calicut.
[3]PharmD, Department of Pharmacy Practice, National College of Pharmacy, Calicut.
[4]PharmD, Department of Pharmacy Practice, National College of Pharmacy, Calicut.
[5]PharmD, Department of Pharmacy Practice, National College of Pharmacy, Calicut.
[6]PharmD, Department of Pharmacy Practice, National College of Pharmacy, Calicut.

ABSTRACT

BACKGROUND

Pneumonia is defined as the inflammation and consolidation of the lung tissue due to an infectious agent. In as many as half of cases, the pathogen remains unidentified which greatly hampers the evaluation of slowly resolving or non-resolving pneumonia.

OBJECTIVE

The main objective is to evaluate the aetiology and clinical profile of non-resolving pneumonia in a tertiary care center and to study the outcome of treatment of non-resolving pneumonia.

DESIGN AND SETTING

A prospective, observational study was carried out in the department of pulmonary medicine of a 700 bedded tertiary care teaching hospital, Kerala.

MATERIALS AND METHODS

The patients who were diagnosed as non-resolving pneumonia were included in the study. Various investigations were done on patients to identify the aetiology and clinical profile of their pneumonia which includes sputum gram stain, culture and sensitivity for bacterial infections, AFB culture, fungal culture, chest X-ray, CT thorax, fibrotic bronchoscopy (For selected patients only) and sputum cytology for malignant cells.

STATISTICAL METHODS USED

Descriptive statistical analysis was done with help of 'Graph pad prism'.

RESULTS

With good clinical interpretations and appropriate treatment, about 31.8% of patients had good clinical improvement and complete chest X-ray clearance after 2 months of follow up where as 36.2% of study subjects had good clinical improvement with incomplete chest X-ray clearance. Majority of this group includes patients who were put on anti-tubercular treatment based on careful interpretation of chest X-ray findings of tuberculosis, Mantoux test and sputum AFB culture results. This implies the importance of early diagnosis of treatable diseases like tuberculosis in our population. Out of the total cases 21.2% of patients had poor clinical outcome whereas 4.4% patients were grabbed by death.

CONCLUSION

Tuberculosis was the commonest cause of non-resolving pneumonia followed by Malignancy. An open mind towards this disease is required and specific investigations are to be made more available.

KEYWORDS

Pneumonia, Non-Resolving Pneumonia, Aetiology, Tuberculosis.

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INTRODUCTION

Medical practitioners have known of pneumonia since ancient times. Hippocrates indoctrinated his students about "Peripneumonia" which for the ancient healers had a connotation of an acute illness either with pain in the side or with severe dyspnoea. The term acquired a more punctilious meaning as the study of morbid anatomy and physical diagnosis progressed over the last few centuries.

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Corresponding Author:
Dr. Binuraj Chathamparamb,
Associate Professor,
Department of Pulmonary Medicine,
KMCT Medical College, Calicut.
E-mail: drbinuraj2005@gmail.com
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Morgani contributed the concept of solidification of the lung. Laennec, the father of pulmonary medicine, described pathological stages of the disease and showed how to diagnose them using auscultation.

Rokitansky's graphic narration helped to distinguish lobar from lobular or bronchial pneumonia. Pasteur discovered streptococcus pneumoniae in 1880, and before long, this organism was proved to be a cause of lobar pneumonia. The contemporary physicians of 19th century were well aware of lobar pneumonia. Coope described lobar pneumonia as that "Which consists of a series of changes by which the spongy pulmonary tissue is rapidly converted into solid mass, returning afterwards, in cases that recover to its normal condition". The modern physician, who is more adept with the X-ray viewing box than the autopsy room, has

acquired sufficient familiarity with this common malady as knowledge and wisdom has been acquired over the centuries. Pneumonia is defined as the inflammation and consolidation of the lung tissue due to an infectious agent.

Normal resolution of pneumonia is variable and depends on the causative agent and host response to the invading agent. In as many as half of cases, the pathogen remains unidentified which greatly hampers the evaluation of slowly resolving non-resolving pneumonia. The terms slowly resolving and non-resolving pneumonia has been used interchangeably to refer the persistence of radiologic abnormalities beyond the expected time course.[1,2] In 1975, Hendin defined slowly resolving pneumonia as pulmonary consolidation persisting more than 21 days.[3]

Originally described by Amberson.[3] in 1943, non-resolving pneumonia has been variably defined. There are several components to successful resolution including clinical improvement, radiologic resolution and microbiologic eradication. In 1991, Kirtland and Winterbauer.[4] defined delayed radio-graphic resolution as less than 50% clearance at 2 weeks or complete clearance at 4 weeks. More recently, Fein and colleagues combined clinical and radiographic indices and defined non-resolving pneumonia as "Slow resolution of radiographic infiltrates or clinical symptoms despite adequate antibiotic therapy".[2] An understanding of risk factors for delayed resolution, the expected resolution time for common pneumonias and the timings and usefulness of further diagnostic studies can help physicians to confidently manage patients with delayed resolution of pneumonia.

OBJECTIVES

To evaluate the aetiology and clinical profile of non-resolving pneumonia in a tertiary care center and to study the outcome of treatment of non-resolving pneumonia.

MATERIALS AND METHODS

A prospective observational study was carried out in the department of respiratory medicine of a tertiary care teaching hospital in Kerala, India. Duration study was 2 years, from May 2013 to April 2015. Patients who were diagnosed as pneumonia by a physician and which are clinically not improved after adequate antibiotic therapy (Empirical antibiotics for 10-14 days) were included in the study.

Inclusion criteria also recommends a chest X-ray report showing <50% resolution after 2 weeks' antibiotic therapy. Patients with smear positive pulmonary tuberculosis and hospital acquired pneumonia were excluded from the study. The selected patients were admitted in the hospital for further evaluation with detailed medical history, clinical examination and investigations.

Various investigations were done on patients to identify the aetiology and clinical profile of their pneumonia which includes sputum gram stain, culture and sensitivity for bacterial infections, AFB culture, fungal culture, chest X-ray, CT thorax, fibre-optic bronchoscopy (For selected patients only) and sputum cytology for malignant cells. The collected data were statistically analyzed using 'Graph pad prism'. Only simple descriptive analysis was needed to conclude the results. Ethical approval was obtained from institutional ethical committee before start of the study. All study subjects were provided with a written informed consent.

RESULTS

A total of 250 patients were screened and 113 patients were recruited to the study. 66.4% of the study population was of age >50 years and most of them were males (69.9%). Patients were categorized in 6 groups according to their provisional diagnosis. Fig. 1 represents the distribution of subjects based on their diagnosis.

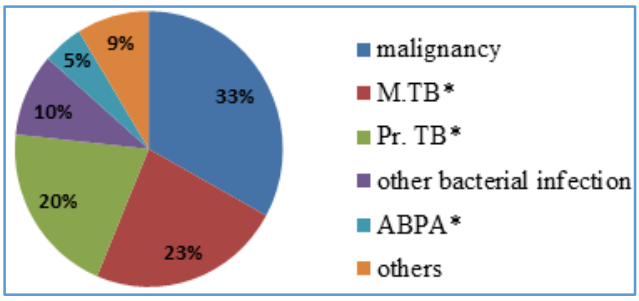

Fig. 1: Distribution of Subjects According to their Provisional Diagnosis

M. TB: mycobacterium tuberculosis, Pr. TB: probable TB, ABPA: allergic bronchopulmonary aspergillosis

Mycobacterium tuberculosis was found to be the leading cause of non-resolving pneumonia. Probable tuberculosis includes those patients who are put on empirical Anti tubercular therapy (ATT) based on chest X-ray findings of tuberculosis and Mantoux test. Others include Bronchiolitis Obliterans Organising Pneumonia (BOOP), Interstitial Lung Disease (ILD), metastasis etc. which is listed in Table 1.

Diseases	No.	Diseases	No.
BOOP	02	Foreign body aspiration	01
Metastasis	02	Acute Myeloid Leukaemia	01
Pulmonary Alveolar Proteinosis	01	Pulmonary infarction	01
Strongyloides	01	Systemic Lupus Erythematosus (SLE)	01
Amiodarone pneumonitis	01	ILD	02
Wegener's granulomatosis	01	Middle lobe syndrome	01
Fungal pneumonia	01	Undiagnosed	03

Table 1: List of other Types of Non-resolving Pneumonia

Various investigations done on study population include sputum examination, chest X-ray, CT scan, pleural fluid study and fine needle aspiration cytology (FNAC). Findings from each test are given below.

Sputum Examination	Number of +ve Result
Acid Fast Bacilli (AFB) Culture	14
Other bacteria in culture	10
Fungal Culture	06
Sputum cytology for Malignant cells	11
Strongyloides.	01
PAS+	01

Table 2: Sputum Examination Results

FNAC Findings	No. of Patients
Malignancy	15
CT Guided FNAC	07
Un guided FNAC	02
FNAC Lymph node	06
Non-specific inflammation	01
Total	**16**

Table 3: Fine Needle Aspiration Cytology Results

FOB (Fibre-Optic Bronchoscopy) Findings	No. of Cases
Malignant Cells in Bronchial brushings & biopsy	25
AFB in Bronchial washings	04
Other Bacterial infections	10
Fungal infections	01

Table 4: Fiberoptic bronchoscopy Findings in Investigated Patients

Sputum examination was diagnostic in 38% of the study population. Total 46 patients were subjected to CT examination with a diagnostic yield of 40.7% pleural fluid study was diagnostic in 8 cases. Fiberoptic bronchoscopic examination was diagnostic in 35.4%, of which majority proved positive for malignancy. Analysis of carcinoma in the study population showed that adenocarcinoma was the common cell type associated with non-resolving pneumonia.

Table 5 illustrates the distribution of carcinomas in the subjects. Organisms associated with non-resolving pneumonia were identified during the study and they are listed in Table 6.

Type of Carcinoma	No. of Patients
Squamous cell Carcinoma	11
Adeno Carcinoma	16
Large Cell Carcinoma	01
Small cell Carcinoma	05

Table 5: Major Cell type of Carcinoma in Study Population

Organisms	Number
S. Pneumoniae	02
Klebsiella pneumonia	02
Pseudomonas aeruginosa	02
Burkholderia pseudomallei	03
Staph. aureus	01

Table 6: Organisms Associated with Non-resolving Pneumonia

Gram negative bacterial infections predominate in the above Table. Clinical outcomes of each patient were assessed after two months of therapy, which reveals that 68% of patients had good clinical outcome after appropriate treatment. Table 7 demonstrates clinical outcomes of therapy.

Outcome	Malignancy	M. TB	Pr. TB	Other Bacterial Infections	ABPA	Others	% Of study Population
Good Clinical + C. Xray clearance	0	10	08	08	05	05	31.8
1+ Incomplete C. Xray Clearance	13	11	12	01	-	04	36.2
Poor Clinical+ C. Xray Clearance	15	03	-	-	-	06	21.2
Lost follow up	03	-	-	-	-	04	06.2
Death in hospital	03	-	01	01	-	-	04.4

Table 7: Clinical Outcomes after 2 Months of Therapy

DISCUSSION

Pneumonia is the sixth leading cause of death and is the most common infectious cause of death. The mortality rate is reported to be 1% in the outpatient setting but it may increase to up to 25% in those requiring hospital admissions. Despite the enormous advance in introduction of antibiotics, delayed resolution of pneumonia is becoming a common problem in clinical practice.

A total of 113 patients were included in the study of which majority of them (66.4%) were over 50 years probably reflecting the fact that they had a lowered immune status than general population and that malignancy was more common in that age group. These were proved in various studies conducted by Van Metre et al.[5] in 1954, Israel et al.[6] in 1956 and jay et al.[7] in 1975 and Mittl & his collegues.[8] Females were only 30% of the study population due to reasons poorly understood, poorly a low prevalence in lung malignancy in females contributed. The diagnostic work-up in our study begins with re-evaluation of initial sputum culture and antimicrobial susceptibility data. Sputum culture was repeated for common bacterial organisms; and also mycobacterial and fungal cultures along with cytological examination for malignant cells were done.

Positive results for bacteria were low (8.8%). These were possibly as a result of an initial course of antibiotics and due to cases that were actually mimics of bacterial pneumonia rather than pneumonia itself. Mycobacterial cultures were positive in 14 cases. In these cases, sputum AFB smears were negative. This data signifies the prevalence of sputum smear negative pulmonary tuberculosis in this community.

In devolving country like India, tuberculosis is the most common entity we always come across. In the present study tuberculosis was found as the most common cause of non-resolving pneumonia. The typical radiographic feature of pulmonary tuberculosis is infiltration with or without cavitation involving apical and posterior segments of upper lobes. Of the total 46 cases of tuberculosis studied, 18 were presented with upper lobe infiltrates in their chest radiographs. Of the total 34 cases of malignancy studied 13 showed lower zone shadow in their chest radiographs with 4 of them had hilar shadow suggesting obstructive pneumonia.

Majority of other cases in our study presented with bilateral infiltrates. Even though chest X-ray said to be no specific investigation, it helped us to reaching on to the right path.

CT scanning affords greater visualization of the lung and surrounding structures and may especially helpful in excluding non-infectious aetiologies. As it is a much costlier investigation it is done only in selected patients.[5] where, other investigations held us in a dilemma in reaching at a diagnosis. In tuberculosis a bilateral diffuse acinar pattern with cavitation especially that cavities not made out from chest X-ray, and bronchiolitis with tree in bud pattern were helpful in diagnosis.

A diagnosis of malignant cell lesion was more directly obtained from CT with mass lesions, obstructive consolidation, mediastinal adenopathy, chest wall involvement etc. In two cases CT features were that of BOOP. HRCT finding of central bronchiectasis was seen in ABPA. In a case of pulmonary alveolar proteinosis CT was showing a crazy pavement pattern. Wegener's granulomatosis CT with multiple cavitating mass lesions and bilateral consolidation was very helpful in reaching at a diagnosis. Two cases of interstitial lung disease were diagnosed with HRCT findings. CT angiography helped in the diagnosis of a case of pulmonary infarction.

Invasive investigation like Mantoux test is not a sensitive test for diagnosing tuberculosis with sputum negativity, but higher values had some specificity for some active disease. Fibre-optic bronchoscopy is invasive but allows direct visualization of the tracheobronchial tree and is often considered in the early evaluation of non in resolving pneumonia. Sterile bronchoscopic cultures may indicate the absence of infection or the adequacy of antimicrobial coverage. Alternatively, persistence of an organism implies resistance and should prompt a change in therapy. Pereira-Gomes and colleages.[9] evaluated the impact of bronchoscopy in 53 cases of non-resolving pneumonia who failed to improve after at least 72 hours of therapy. They frequently isolated organisms like Acinetobacter baumannii(38.7%), S aureus (19.3%) and P aeruginosa(17.7%) and the BAL cultures resulted in making changes in antibiotic therapy in most patients and helped them in achieving significant reduction in mortality.

The diagnostic yield for bronchoscopy in our study was 35.4% of which majority (25) cases proved positive for malignancy, 10 of them diagnosed as bacterial infection, 4 tuberculosis and one fungal infection. But a previous studies malignancy was found to be an unusual cause for non-resolving pneumonia.[6,7,9] From our study of the malignancies proved by bronchoscopy 16 patients had endobronchial lesions of which 11 cases were squamous cell carcinoma and 5 were small cell carcinoma. All of these patients had high smoking score and they presented with features of obstructive pneumonia. The increase prevalence of malignancy may be due to high smoking score in the study population.

Other invasive investigation which was found useful in diagnosis in our studies includes fine needle aspiration cytology and pleural fluid study. 15 cases of malignancies and 1 case of Burkholderia pseudomallei were evolved with the help of FNAC. Pleural fluid study helped in differentiating mycobacterium tuberculosis from other bacterial infections. Fang et al in his prospective study reported Haemophilus was the second most frequently isolated pathogen because it is a frequent colonizer of upper respiratory tract and is readily cultured from sputum of individuals without pneumonia.

Legionella was the third most commonly isolated pathogen in Fang study [10]. Failure of eradication is most common among infections with high risk organisms such as Pseudomonas, Acinetobacter and MRSA. Fagon and colleagues.[11] reported an increased mortality and hospital length of stay among patients infected with these pathogens.
In our study Klebsiella pneumonia and Pseudomonas aeruginosa shared 2 cases each. Of the total, 3 were Burkholderia pseudomallei and 1 case of MRSA contributes their aetiology in non-resolving pneumonia. These patients were all elderly and also diabetic which predisposes to the condition.

The clinicians often considers malignancy when pneumonia fails to resolve, however, several studies.[12,13] have reported it to be an infrequent cause of non-resolving pneumonia. In their series of 115 patients with non-resolving and chronic pneumonia, Kirtland et al.[1] reported an incidence of 19%. This value is much higher than that reported in other series, and the inclusion of chronic pneumonias may explain the discrepancy. BAC is most notorious for mimicking a pneumonic process but infrequently presents with diffuse infiltrates.

Systemic illness like diabetes, co-infection with HIV also doubles the incidence of tuberculosis. In our study also even after the exclusion of sputum smear positive pulmonary tuberculosis cases, it was found to be the most common cause of non-resolving pneumonia (39.8%). So a high index of suspicion for tuberculosis should be kept in mind while dealing with a case of non-resolving pneumonia.

An association between smoking and lung cancer has been established through various studies which reveal the importance of arranging smoking cessation program in the community.

The incidence of non-infectious conditions mimicking pneumonia is variable. The various aetiologies evolved from our study were ABPA (5 cases), BOOP (2 cases), Pulmonary alveolar proteinosis (1 case), Strongyloides (1 case), Amiodarone pneumonitis (1 case), Wegener's granulomatosis (1 case), Acute myeloid leukaemia (1 case) and so on.

With good clinical interpretations and appropriate treatment, about 31.8% of patients had good clinical improvement and complete chest X ray clearance after 2 months of follow up where as 36.2% of our study subjects had good clinical improvement with incomplete chest X-ray clearance. Majority of this group includes patients who were put on anti-tubercular treatment based on careful interpretation of chest X ray findings of tuberculosis, Mantoux test and sputum AFB culture results. This implies the importance of early diagnosis of treatable diseases like tuberculosis in our population. Out of the total cases, 21.2% of patients had poor clinical outcome whereas mortality was about 4.4%. This includes those patients diagnosed as having malignancy with end bronchial occlusion and with specific risk factors like smoking history, advanced age, other comorbidities and those who had end stage lung diseases at the time of diagnosis.

So in short understanding the infectious and non-infectious causes of pneumonia and their normal times to resolution and the knowledge of various risk factors will be enormously helpful in the judicious evaluation of and timely intervention in this very challenging condition.

CONCLUSION

Tuberculosis was the commonest cause of Non-resolving pneumonia followed by Malignancy. The less common causes of pneumonia and other mimics of pneumonia are also being recognized. With appropriate treatment, 68.2% of patients had good clinical outcome. 32.8% patients had poor clinical outcome. Invasive procedures may be required more frequently for reaching at the diagnosis along with non-invasive approach. A comprehensive approach and an array of diagnostic techniques are required to make the proper diagnosis.

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