DOI: http://dx.doi.org/10.24327/ijcmes2017.07030001

Available online at http://journalijcmes.com

INTERNATIONAL JOURNAL OF CURRENT MEDICAL SCIENCES

RESEARCH ARTICLE

ISSN: 2320- 8147

International Journal of Current Medical Sciences- Vol. 7, Issue, 03, pp. 225-228, March, 2017

NON TUBERCULOUS MYCOBACTERIA INFECTION IN BRONCHIECTASIS PATIENTS

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A R T I C L E I N F O

Article History:

Received 10th, December, 2016,
Received in revised form 7th,
January 2017, Accepted 26th, Februray, 2017,
Published online 28th, March, 2017

Key words:

Non tuberculous mycobacteria, Bronchiectasis, Tuberculosis

A B S T R A C T

Background: Bronchiectasis patients are predisposed to infection with non tuberculous mycobacteria (NTM) but the exact prevalence of the disease is unknown, which may be higher than anticipated because of the non-specific symptoms and routine screening is not usually undertaken. The aim of the current study was to determine prevalence of non tuberculous mycobacterial infection in bronchiectasis patients.

Methods: A prospective study of fifty two patients with bronchiectasis irrespective of segments involved, having sputum for acid fast bacilli negative and willing to undergo fibreoptic bronchoscopy was taken. AFB Culture and Para nitro benzoic acid test for NTM were done in BAL sample.

Results: Out of fifty two patients, twenty eight (53.85%) were males and twenty four (46.15%) females. Eleven (21.2%) were positive for NTM in the study. Males positive for NTM had higher mean age (54.67yrs vs. 46yrs). Five (45.45%) NTM positive patients had history of anti-tubercular therapy (ATT) intake. Seven patients were positive for rapid growers (M. abcessus) and four for slow growers (MAC).

Conclusions: Bronchiectasis leads to NTM infection or vice versa is not possible to cite upon as symptom profile is similar. In the present study M.abcessus were twice as common as MAC in presence of bronchictasis. About one-fifth of patients in the study were positive for NTM having a significant association implying the importance of ruling out NTM in bronchiectasis patients.

INTRODUCTION

Bronchiectasis (ectasia meaning dilatation and bronchos meaning of the airways) is defined as an abnormal, irreversible dilatation of the bronchi. Bronchiectasis is 'not a separate disease but a result of various affections of the lungs and bronchi'.[1,2] Bronchiectasis has varied causes which include post infectious, congenital, abnormal immune defense ,bronchial obstructions etc. The most widely known model of the development of bronchiectasis is Cole's "vicious cycle hypothesis".[3] In this model, Cole proposed that an environmental insult often on a background of genetic susceptibility impaired muco-ciliary clearance resulting in persistence of microbes in the sinobronchial tree and microbial colonization.

Bronchiectasis patients are predisposed to infection with non tuberculous mycobacteria (NTM) but the exact prevalence of the disease is unknown.[4] Non tuberculous mycobacteria (NTM) are ubiquitous environmental organisms that sometimes cause respiratory disease, usually in patients with preexisting lung damage.[5] Patients with bronchiectasis, as with other chronic lung diseases, are predisposed to infection with NTM. The prevalence of nontuberculous mycobacteria (NTM) both in environment and as pathogens varies in different parts of the world. The symptom profile of NTM pulmonary infection such as increased sputum production, cough, breathlessness and haemoptysis is similar to bronchiectasis, making differentiation between active infection and colonisation difficult. Furthermore, some NTM infections cause bronchiectasis, so a radiological diagnosis of NTM infection is difficult to make in the presence of underlying disease.

NTM are inhaled as aerosol droplets so may be cultured if a sputum sample is obtained soon after environmental exposure. According to American thoracic criteria for NTM, 2 sputum samples should be positive for NTM in 2 different occasions or 1 bronchial washing or lavage specimen in a clinico radiologically relevant patient

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reflecting the poor sensitivity of sputum sample in diagnosing NTM infection and thus low prevalence.[6]

HRCT has proved to be diagnostic for bronchiectasis and may also suggest an aetiology for the same. Identification of NTM infections aetiologies has also advanced due to improvements in diagnostic methods.[7] Despite the advancements in diagnostics, the diagnosis is often delayed as symptom profile of NTM infection is similar to bronchiectasis, so an active search for NTM is not carried out. Also tuberculosis has a similar symptom profile and sputum for acid fast bacilli smear may be positive in NTM infections also and thus disease may be misdiagnosed as TB.[8,9]

Few studies have undertaken a detailed analysis of NTM in the context of bronchiectasis. The prevalence of NTM in bronchiectasis may be higher than anticipated because of the non-specific symptoms and because routine screening is not usually undertaken.[5] In one study, three cases of NTM were detected over 6 years in 91 patients with bronchiectasis.[10] In another, NTM were found in 6% of bronchiectatic patients.[11] In a study from eastern asia, NTM Prevalence was estimated to be around 31% in respiratory tract infections.[12]

As there is little information regarding prevalence of NTM infection and in bronchiectasis patients as a whole in North-eastern region of India, this study was undertaken to determine the prevalence of NTM infection in bronchiectasis patients.

MATERIALS AND METHODS

It was an institutional based prospective study undertaken in department of Pulmonary Medicine, Gauhati Medical College and Hospital in Guwahati, Assam. The patients attending the Out Patient Department or admitted during the period of one year from December 2015 to January 2016 were selected for the study. Patients were included in the study if they were more than 14 years old and had radiological changes suggestive of bronchiectasis on Computed Tomography of chest. The radiographic findings consistent with bronchiectasis include morphologic abnormalities associated with bronchial dilatation, typically described as cylindrical, varicose or cystic; internal diameter greater than adjacent pulmonary artery; lack of bronchial tapering; visibility of airways in the peripheral lung zones; bronchial wall thickening and irregularity; presence of mucous impaction of the bronchial lumen, bronchiolectasis.[13]

Patients were excluded from the study if they were not willing to give consent, had smear positive Pulmonary tuberculosis and patients with contraindications for bronchoscopy like patients with hypoxia, uncontrolled arrhythmia , unstable cardiac status. Consent was taken from all the patients. All patients included in the study underwent flexible fiberoptic bronchoscopy (FOB) and bronchoalveolar lavage (BAL) was taken from radiological abnormal segments. FOB was performed under local anaesthesia and spray as you go technique while in the airway. Microbiological tests like acid fast bacilli smear and culture, para nitro benzoic acid test (PNB)(8), gram stain and culture sensitivity and fungal smear was performed in all the cases.. PNB test was performed for detection of NTM and species were identified by the growth characteristics, including growth at 25, 37 and 42 °C, pigment production, semi-quantitative catalase test, Tween 80 hydrolysis, arylsulfatase test (3 and 14 days), heat-stable catalase (pH 7, 68 °C), pyrazin amidase (4 and 7 days), urease, nitrate reduction test and colony morphology.

The following data were collected for the patients included in the study: (1) demographic data like age, sex, (2) characteristics of the symptoms like cough, haemoptysis, dyspnea, chest pain and other symptoms, (3) smoking habits, (4) history of anti tubercular therapy intake, (5) routine laboratory investigations, (6) radiology findings, segments involved, unilateral or bilateral and (8) microbiology results.

HRCT Thorax has been divided into four categories: middle lobe and /or associated segments; lingula and/or associated segments; middle lobe and lingula; widespread. Widespread denotes involvement 2 or more lobes.

Statistical analysis – Categorical variables were described as counts or percentages. Group comparisons were made using x^2 or Fisher's exact test as appropriate. A p value of 0.05 was regarded as statistically significant. For group comparisons, Tukey test with one way ANOVA analysis was applied.

RESULTS

Fifty two patients who provided consent were included in the study. Eleven patients were positive for NTM infection. Table 1 shows the characteristics of the patients positive and negative for NTM infection.

Table 1 Characteristics of patients enrolled in the study

Demographics	NTM positive n (%)	NTM negative n (%)	P value
Patients	11 (21.15)	41 (78.85)	
Males	6 (11.54)	22 (42.31)	1.00
Female	5 (9.62)	19 (36.54)	
Age ≥ 40 years	11 (21.15)	24 (46.15)	0.0098
Mean age in years ± SD	50.73 ± 9.02	42.95 ± 13.0	
Non Smoker	10 (19.23)	35 (67.31)	1.00
ATT intake	5 (9.62)	16 (30.77)	0.7395
Cough present	10 (19.23)	32 (61.54)	0.6678
Haemoptysis present	10 (19.23)	32 (61.54)	0.6678
Dyspnea present	4 (7.69)	12 (23.08)	0.7195

The average age of the bronchiectasis patients was 44.60 ± 12.60 years. The minimum age of the patient in the study was 19 years while the maximum age was 70 years. The mean age of the patients positive for NTM infection was 50.73 years while that of negative patients was 42.95 years. All patients positive for NTM infection had age more than or equal to 40 years and p value was <0.05.

Out of 52 patients, 28 were males and 24 females. Of 11 positive patients, 6 were males and 5 females. The mean age of the male patients positive for NTM infection was 54.67 years vs. females positive had 46 years. Tukey test with one way ANOVA performed for comparison of means was not significant. Twenty-one patients (40.38%) had history of Anti Tubercular therapy, of whom five were

positive for NTM. All male patients positive for NTM had history of cough and hemoptysis and on the other hand 80% female patients positive for NTM had history of cough and hemoptysis. All were non-smokers, except for seven males of whom one was positive for NTM. The clinical characteristics of the patients in NTM positive and NTM negative groups were not significant for history of ATT intake, smoking, presence of cough, haemoptysis and dyspnea. The clinical variables did not differ significantly in between male and female patients also.(Table-2)

Table 2 Characteristics of male and female patients

Characteristics	Males		Females		P value
Ntm infection	Positive	Negative	Positive	Negative	
Patients No.	6	22	5	19	
Mean Age ± SD(in years)	54.67 ± 8.38	40.81 ± 12.76	46 ± 8.03	45.42 ± 13.17	0.1103
Smoking History	1 (16.67%)	6 (27.27%)	Absent	Absent	
Att Intake History	3 (50%)	8 (36.36%)	2 (40%)	8 (42.11%)	0.9399
Cough Present	6 (100%)	16 (72.73%)	4 (80%)	16 (84.21%)	0.4769
Hemoptysis Present	6 (100%)	18 (81.82%))	4 (80%)	14 (73.68%)	0.3577
Dyspnea Present	2 (33.33%)	7 (31.82%)	2 (40%)	5 (26.31%)	0.9388

Eleven (21.2%) patients were positive for NTM, seven for rapid growers (4 males, 3 females) and four for slow growers (two each in male and female). Four rapid growers were identified as Mycobacterium abscessus and two slow growers as Mycobacterium intracellulare while the rest of the species identification could not be done. In NTM negative patients, three patients were positive for staphylococcus aureus, three for pseudomonas aeruginosa and one patient for klebsiella in gram stain & culture. (Table-3)

Table 3 Types of NTM

	Rapid Grower	Slow Grower
Male	4	2
Female	3	2
Total	7	4

Table 4 Bronchiectasis distribution in HRCT thorax in NTM positive and negative patients

Bronchiectasis distribution	NTM Positiv	NTM Negative	P value
Widespread	4	13	1.00
Lingula (and/or associated sements)	2	7	1.00
Middle lobe (and/or associated sements)	3	8	0.4795
Middle lobe and Lingula	2	13	0.6810
OTHER FINDINGS			
Nodules	2	11	
Mucoid impaction	7	1	
Ground glass opacity	4	0	
Fibrotic changes	5	2	
Consolidation	3	0	

Table 4 shows the bronchiectasis distribution in HRCT thorax in NTM positive and negative patients. Out of 11 positive patients widespread bronchiectasis was found in 4 patients, Middle lobe (and/or associated sements) bronchiectasis in 3 patients and 2 patients each in lingula segment and two in middle lobe/lingula segment. There was no statistically significant bronchiectasis distribution in HRCT among NTM positive and negative patients. In table 5, distribution of bronchiectasis in patients positive for NTM is shown along with type of NTM, rapid (RG) or slow growers (SG). Out of 7 NTM rapid growers 3 were positive in widespread bronchiectasis and 2 in middle lobe and lingula bronciectasis. Out of 4 slow growers, 2 were positive in Middle lobe (and/or associated sements). Distribution of bronchiectasis on HRCT Thorax did not have any statistical significance with patients positive for NTM with any particular segment or lobe involvement though involvement of middle lobe or lingular segment had higher positivity.

Table 5 Distribution of bronchiectasis in patients positive for NTM

Bronchiectasis distribution	All isolates	Rapid grower	Slow grower
Widespread	4	3	1
Lingula (and/or associated sements)	2	1	1
Middle lobe (and/or associated sements)	3	1	2
Middle lobe and lingual	2	2	0

DISCUSSION

In the present study, prevalence of NTM infection in bronchiectasis was around 21% and there was no gender predilection with equal occurrence in both males and females. NTM infection was predominant in elderly persons as all cases had age more than 40 years with rapid growers as the predominant organism.

High prevalence of NTM infection in the present study was in concordance with a study on non-CF bronchiectasis patients where they reported prevalence of 30%.(8) In another study by Simons *et al*.(12) on prevalence of NTM infections in eastern asia population they stated 31% as prevalence rate. This was in contrast to studies of Wickremasinghe *et al*[5] who found prevalence of 2% NTM infection in bronchiectasis patients. Palatwichai *et al*[11] in their study on Thai bronchiectasis patients stated a prevalence rate of 6%.

Bronchiectasis and NTM association has been predominantly seen in females.(14) This finding was also seen in studies by Wickremasinghe *et al*[5], Mirsaeidi *et al*[8] where females had greater association of bronchiectasis and NTM infection. This association was not seen in the present study where gender predilection had no statistical significance. In various studies, mean age of the patients positive for NTM were >60years,[5,8] a finding which was not corroborated in the present study. In this study, mean age of the NTM infection positive male patients was 50 years with female positives having a mean age of 46 years which was in contrast to other studies.

Almost 40% patients had history of anti tubercular therapy intake, of whom 25% were positive for NTM. Symptom profile of the NTM positive and negative patients were similar in the present study. Cough and haemoptysis being the predominant symptom, which can be presentation of either NTM or bronchiectasis. Dyspnea was seen in a small number of patients and was not statistically significant. The above symptoms may also be seen in tuberculosis, a diagnosis much more common in our

country and can thus mask or obviate the need of further investigations in a patient.

In our study, distribution of bronchiectasis on HRCT thorax and patients being positive for NTM infection had no statistical significance, though involvement of middle lobe or lingula or both with or without associated segments/lobes had greater positivity. Mucoid impaction and consolidation were two features predominantly seen in NTM positive patients. Out of 11 positives, 7 were positive for rapid growers and 4 for slow growers. Mycobacterium abscessus(4 patients) and mycobacterium intracellulare(2 patients) were the organisms isolated in rapid grower and slow growers groups respectively. In 5 patients species identification could not be done. Though MAC is the predominant organism isolated worldwide, (6,12,15) this view was not shared with the present study and in some studies from India, Taiwan and south korea where rapid growers had 30% prevalence.(12)

In the present study, six patients positive for NTM agreed to undergo treatment. But due to the long duration and cost of therapy, only three patients were compliant with treatment at the end of 1 year and they reported an improvement in their symptoms.

CONCLUSION

In the present study, NTM was commonly isolated in bronchiectasis patients with Rapidly growing mycobacteria being more common in this group. No predilection for males or females was seen in this study. Patients with age >40years were seen to be significantly associated with NTM positivity in the present study and half of the positives had history of anti tubercular therapy. In this small study it is difficult to comment whether NTM lead to bronchiectasis or vice versa.

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