

Impact Of Bronchiectasis On COPD Exacerbations

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Abstract

The presence of bronchiectasis is considered an aggravating factor in COPD patients. In particular, the coexistence of bronchiectasis and COPD was associated with greater frequency and severity of exacerbations.

The aim of this study is to investigate the impact of bronchiectasis in patients with COPD exacerbation.

We retrospectively collected data from 212 patients admitted to the hospital with diagnosis of COPD exacerbation. In order to detect the presence of bronchiectasis, only patients that had received a chest HRCT scan examination were included in the study. We compared clinical and functional data between COPD patients with bronchiectasis and those without bronchiectasis.

The prevalence of bronchiectasis was 31,6% in this study. The presence of bronchiectasis in COPD patients was associated with increased risk for isolation of PPMs in the airway (56,1% vs 28,3%, p 0,02), and in particular of *Pseudomonas Aeruginosa* (17,5% vs 5,6% p 0,02), and with a longer duration of hospitalization ($8,22 \pm 3,67$ vs $6,88 \pm 3,43$ days, $p=0.004$).

These results could encourage efforts to optimize medical care for patients with COPD and bronchiectasis. Clinical trials with treatments for infective component are needed to investigate their impact on the reductions of exacerbations and improvements in the disease course.

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Keywords: COPD, Bronchiectasis, exacerbations

Received: Jan 27, 2018

Accepted: Apr 04, 2018

Published: Apr 07, 2018

Editor: Mohamed Shahat Badawy Ahmed, Assistant Professor of Chest Diseases Head of Chest Department, Qena Faculty of Medicine, South Valley University, Egypt.

Introduction

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of morbidity and mortality worldwide with a substantial social and economic burden [1]. It's a complex disease with different clinical features and treatment responses [2-6]. In recent years, there has been a growing interest in identifying COPD phenotypes, in order to provide more individualized treatment strategies [2-6]. High-resolution computed tomography (HRCT) of the lungs may provide a way to define a distinct COPD phenotype by investigating the main relevant morphological findings such as the presence of emphysema, bronchial wall thickening, and bronchiectasis [9-12].

Bronchiectasis is defined as irreversible and generally progressive dilation of the airways, usually as a result of chronic airway inflammation and/or infection.

The impact of bronchiectasis on COPD was assessed in several studies [13-16]. Determining the precise prevalence of bronchiectasis in COPD is difficult; existing data indicate a huge variability in bronchiectasis prevalence, ranging from 4 to 72%. However, there is agree to consider bronchiectasis an aggravating factor in COPD patients [11-16].

Bronchiectasis was defined as a comorbidity of COPD [1], nevertheless this definition may be reductive. In fact, the coexistence of bronchiectasis and COPD may properly suggest a different clinical COPD phenotype [1,15,21]. In particular, the presence of bronchiectasis in COPD has been associated with greater frequency and severity of exacerbations [22-24].

An exacerbation of COPD is defined as sustained worsening of respiratory symptoms, such as breathlessness or increased sputum volume or purulence beyond the basal variability and that required treatment with oral corticosteroids or antibiotics [1,25]. Patients with mild or moderate COPD exacerbation can be managed at home, while patients with severe symptoms may need hospitalization [1,25]. Hospitalizations for COPD exacerbation are associated with increased mortality and impaired health-related quality of life. Furthermore hospitalizations for COPD exacerbation account for more than 70% of all COPD-related health care costs [1,25].

In this study we aim to analyze the impact of bronchiectasis on patients with COPD exacerbation.

Methods

In this retrospective study we collected data from 212 consecutive patients admitted to the Pneumology Unit of Monaldi Hospital in Naples between 2010 and 2014, with diagnosis of exacerbation of COPD. In order to detect the presence of bronchiectasis, only patients that had received a chest HRCT scan examination were included in the study. Written informed consent was obtained from all of the patients. The study was approved by hospital Ethic Committee.

Clinical characteristics were recorded for each patient, including lung function, smoking history, comorbidities and number of COPD exacerbations in the previous year.

COPD was confirmed by the presence of a post-bronchodilator forced expiratory volume in 1 second/forced vital capacity (FEV1/FVC) < 70% according to the criteria published by the GOLD document [1].

COPD exacerbation was defined as an acute event characterized by a worsening of the patient's respiratory symptoms that results in additional therapy [1].

The diagnosis of bronchiectasis was confirmed by a chest HRCT scan. High-resolution images were obtained in full inspiration at 1-mm collimation and 10-mm intervals from the apex to the base of the lungs. Based on the morphology, bronchiectasis was defined as cylindrical, cystic and mixed.

α 1-antitrypsin deficiency, serum immunoglobulin deficiencies, IgE and IgG to *Aspergillus fumigatus* and cystic fibrosis were excluded in all patients with bronchiectasis.

During hospitalization each patient was requested to collect samples of spontaneous mornig sputum for the microbiologic analysis. Samples were processed by the reference clinical microbiology laboratory using standard procedure [26-29]. The suitability of the sputum sample for the culture was assessed with Q score, examining leukocytes and epithelia cells by gram stain (Q1: 0 epithelial cells and 1-9 leukocytes per field or < 10 epithelial cells and

10-24 leukocytes per field or < 25 epithelial cells and >25 leukocytes. Q2: 0 epithelial cells and 10-24 leukocytes per field or 1-9 epithelial cells and > 25 leukocytes per field. Q3: 0 epithelial cells and > 25 leukocytes per field) [26,27].

Samples with a Q score ≥ 1 were considered representative of distal airways and subsequently processed for culture. Bacterial growth was assessed at 48 hours and fungal growth at 72 hours. The airway bacteria cultured were classified into potential pathogenic microorganisms (PPMs) and non-PPMs, as previously described [28].

Based on previously published methods, sputum cultures were expressed as colony-forming units (CFUs) per mL and a cutoff point of 10^3 CFUs/mL or more was defined as significant for the identification of abnormal positive culture results for PPM [29]. Isolated bacterial agents were classified into PPMs strains, including *Pseudomonas Aeruginosa*, *Streptococcus Pneumoniae*, *Moraxella Catarrhalis*, *Haemophilus Influenzae*, *Staphylococcus Aureus*, *Klebsiella pneumoniae*, *Escherichia coli*, *Mycobacterium tuberculosis*, *Candida albicans* and other pathogenic microorganisms.

Statistics

The statistical software SPSS, version 20, was used for the statistical analysis. The Student T test for independent variables was used to analyze variables that were normally distributed and the Mann-Whitney U test was used to analyze variables that were non-normally distributed. The chi-square test was used to compare qualitative variables. A p-value less than 0.05 was considered to be statistically significant.

Results

Overall, data from 212 patients with COPD exacerbation were retrospectively analyzed (mean age \pm SD $71,3 \pm 8,5$; 79,2% men). Based on HRCT evidence of bronchiectasis, the patients were divided into two groups: patients with bronchiectasis (n=67, 31,6%) and patients without bronchiectasis (n=145, 69,4%). Other conditions that can trigger bronchiectasis were excluded (α 1-antitrypsin deficiency, serum immunoglobulin deficiencies, IgE and IgG to *Aspergillus fumigatus*, cystic fibrosis). Bronchiectasis was cylindrical in 85% of cases.

Clinical and functional data were compared between the two groups.

The entire patient population had moderate to severe COPD.

The presence of bronchiectasis was associated with a higher number of exacerbations in the previous year (p 0,00001).

The smoking history, expressed as pack/years, was more significant in COPD patients without bronchiectasis (p 0,0001).

FEV1, FVC, PaO₂, PaCO₂ of patients, as well as the Charlson Index score, didn't significantly vary between the two groups. An average of 3 valid sputum samples was collected from patients who had daily sputum production during the hospitalization. COPD patients with bronchiectasis had a higher prevalence of PPMs colonization (p=0,02). *Candida Albicans* was the most frequently isolated PPM in the entire patient population (62 patients). The isolation of *Pseudomonas Aeruginosa* was significantly most frequent in COPD patients with bronchiectasis than in those without bronchiectasis (p=0,02), while the isolation of other PPMs was not significant different between the two groups. *Mycobacterium tuberculosis* and nontuberculosis mycobacteria weren't detected in any samples.

No samples or unqualified samples were collected from 49 patients (23,1%).

The presence of bronchiectasis in patients with COPD was associated with a longer duration of hospitalization ($8,22 \pm 3,67$ vs $6,88 \pm 3,43$ days, p=0.004)

The differential characteristics of the two groups are reported in tables 1 and 2.

Discussion

In this small study, we evaluated the impact of bronchiectasis on patients with COPD exacerbation.

The prevalence of bronchiectasis in COPD patients was 31,6%. This finding is similar to the percentage reported in previous studies [6-11]. 85% of patients had cylindrical bronchiectasis. Although there is still much to understand about the interaction between COPD and bronchiectasis, the high rate of coexistence of bronchiectasis and COPD could be explained by shared

Table 1. Baseline and clinical characteristics of subjects with COPD, with and without bronchiectasis. Data are presented as n (%) or mean \pm SD. (Statistical tests: T-student test, Mann-Whitney Test)

	Whole Group	COPD with Bronchiectasis	COPD without Bronchiectasis	p
Subjects	212	67 (31,6%)	145 (68,39%)	
Sex, M/F	168/44	119/26	49/18	
Age, Y	71,33 \pm 8,48	69,97 \pm 9,8	71,48 \pm 9,61	0,11
Smoking History-pack/years	24,95 \pm 10,78	20,3 \pm 10,19	27,18 \pm 10,28	0,0001
Number of Exacerbations in the previous year	1,14 \pm 0,8	1,57 \pm 0,74	0,94 \pm 0,75	0,00001
FVC	63,33 \pm 14,66	60,94 \pm 12	64,44 \pm 15,66	0,1
FEV1	46,84 \pm 13,55	46,59 \pm 10,53	46,96 \pm 14,75	0,85
pO2 mmHg	62,97 \pm 11,4	62,08 \pm 10,38	63,39 \pm 11,34	0,42
pCO2 mmHg	57,04 \pm 13,91	43,30 \pm 7,58	44,32 \pm 7,15	0,34
Charlson Index	2,16 \pm 0,68	2,06 \pm 0,69	2,21 \pm 0,66	0,15
Length of hospitalization	7,30 \pm 3,55	8,22 \pm 3,67	6,88 \pm 3,43	0,004

Table 2. Microbiological characteristics of subjects with COPD, with and without bronchiectasis. Data are presented as n (%) or mean \pm SD. (Statistical test : Chi-Square)

	Whole Group 163	COPD with Bronchiectasis 57	COPD without Bronchiectasis 106	p
Haemophilus Influenzae	26 (15,9%)	8(14%)	18 (16,9%)	0,6
Streptococcus Pneumoniae	17 (10,4%)	5 (8,7%)	12 (11,3%)	0,6
Moraxella Catarrhalis	16 (9,8%)	5(8,7%)	11(10,3%)	0,7
Pseudomonas Aeruginosa	16 (9,8%)	10 (17,5%)	6 (5,6%)	0,02
Staphiloccocus Aureus	7 (4,2%)	4(7%)	3 (2,8%)	0,2
Escherichia Coli	6 (3,6%)	3 (5,2%)	3 (2,8%)	0,4
Klebsiella Pneumoniae	4 (2,4%)	2 (3,5%)	2 (1,8%)	0,5
Candida Abicans	62 (38%)	18 (31,5,8%)	44(41,5%)	0,3
Patients with at least one PPM isolate	62 (38%)	32 (56,1%)	30 (28,3%)	0,02

pathological mechanisms. In fact, chronic inflammation of airway has a key role in the pathogenesis of both conditions and tobacco exposure is considered a causal factor in both diseases[30-33]. The presence of bronchiectasis in COPD patients was associated with a greater number of exacerbations in the previous year. The association between bronchiectasis and a greater frequency of exacerbations is widely recognized [22-24]. This is probably due to permanent dilatation of the airways and impairment of mucociliary clearance that can lead to bacterial colonization. Bacterial colonization can trigger an intense inflammatory response which damages local defense mechanism. This interaction between chronic PPM colonization and systemic inflammation may lead to frequent exacerbations, as well as other distinctive clinical features as more sputum production [24].

About pulmonary function data, the entire patient population had moderate to severe COPD.

FEV1 didn't significantly vary between the two groups. This result is opposite to the findings of previous studies in which bronchiectasis was associated with more severe bronchial obstruction[18-20]. This discrepancy may be explained by several reasons. Firstly, the small sample size in the present study provides insufficient statistical power. Secondly, in this study, COPD patients with bronchiectasis had a less significant smoking history. The presence of bronchiectasis was associated with increased prevalence of PPMs colonization and in particular of *Pseudomonas Aeruginosa*. The association of chronic PPMs colonization, as well as *P. Aeruginosa* isolation, with bronchiectasis was confirmed by several studies [22-24,34]. The presence of PPMs and the consequent chronic inflammation result in remodeling of the airways and facilitate the persistence of PPMs in the bronchial tree. These factors may trigger the mechanism that generates bronchiectasis [15,35]. Furthermore, *Pseudomonas Aeruginosa* was isolated from 3% to 20% of patients with COPD and, more frequently, from patients with severe disease and during exacerbations [37]. COPD patients with bronchiectasis had a longer length of hospitalization. This is may be justified by the need of more prolonged antibiotic therapies. Considering these data and the higher

frequency of exacerbations, it's clear that the detection of bronchiectasis in COPD by performing an HRCT scan should be encouraged in order to identify these patients and provide the most effective treatment. The coexistence of bronchiectasis and COPD should expect more appropriate treatment for the infective component of the disease. Unfortunately, data about therapies for COPD complicated by bronchiectasis are not available, due to the lack of clinical trials in this population. Based on trials on bronchiectasis, including smokers with airflow obstruction which is not fully reversible and similar to COPD, some Authors have suggested that the use of long-term macrolides or inhaled antibiotics could be beneficial in reducing exacerbations in COPD patients with bronchiectasis. Physiotherapy should also be considered as an useful strategy in these patients [15,36,37].

The presence of bronchiectasis in COPD patients has a significant impact on disease course as well as on economic burden on the healthcare system. A substantial portion of the total burden of COPD is related to exacerbations, in particular to hospitalization[1,39]. Based on our results, the coexistence of bronchiectasis and COPD leads to higher health care costs (longer hospitalizations, more prolonged antibiotic therapies].

Conclusion

In conclusion, data obtained from the present study indicate that the presence of bronchiectasis in patients with COPD exacerbation was associated with an increased risk of isolation of PPMs, in particular of *Pseudomonas Aeruginosa*, and with a longer duration of hospital stay. These results could encourage efforts to optimize medical care for patients with COPD and bronchiectasis. Clinical trials with treatments for infective component are needed to investigate their impact on the reductions of exacerbations and improvements in the disease course.

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