ORIGINAL ARTICLE

Investigation of bronchiectasis in severe uncontrolled asthma

Katerina Dimakou | Anna Gousiou | Michail Toumbis | Maria Kaponi | Serafeim Chrysikos | Loukas Thanos | Christina Triantafillidou

1 5th Pulmonary Department, “Sotiria” Chest Diseases Hospital, Athens, Greece
2 American College of Greece (Deree), Aghia Paraskevi Campus, Athens, Greece
3 6th Pulmonary Department, “Sotiria” Chest Diseases Hospital, Athens, Greece
4 Department of Radiology, “Sotiria” Chest Diseases Hospital, Athens, Greece

Correspondence
Christina Triantafillidou, Mesogeion 152, 11527, Athens, Greece.
Email: xristina.triantafyllidou@gmail.com

Abstract

Introduction: The presence of bronchiectasis in patients with asthma varies in different reports, while a clear aetiological relation has not been precisely established.

Objectives: To investigate the presence of bronchiectasis in patients with severe uncontrolled asthma and examine whether they contribute to the severity of asthma.

Methods: Patients with severe asthma were prospectively recruited. HRCT of the chest was performed to identify and grade bronchiectasis using the ‘Smith’ radiology scale. Investigation of the underlying cause was carried out for patients with bronchiectasis in order to exclude aetiologies other than asthma. The Statistical Package for the Social Sciences (SPSS), version 21, was used.

Results: Forty patients were studied, 28 women, mean age (±SD) 57.9 years (±12.4). Mean ACT score was 14.2 (±4.9). Main symptoms were: wheezing (95%), cough (92%), dyspnea (92%) and sputum production (72%). Mean duration of asthma was 16.5 (±11.5) years, exacerbations: 4.4 (±2.7)/year. In 27 patients (67.5%) bronchiectasis was diagnosed. In nine patients (22.5%) pathogens were cultured in sputum (mainly Pseudomonas aeruginosa, Haemophilus influenzae). Patients with sputum production and pathogen isolation in sputum cultures had a higher Smith score compared to those without expectoration and without pathogens, respectively (P = .005, P < .0001). No correlation was found between the extent of bronchiectasis and lung function. The radiological severity of bronchiectasis was correlated with the antibiotic courses/year (P = .002).

Conclusion: Bronchiectasis is common in patients with severe asthma. Sputum production and pathogen isolation in sputum may indicate the presence of bronchiectasis which seems to contribute to the severity of asthma.

KEYWORDS
antibiotics, asthma, bronchiectasis, exacerbation, pathogens, sputum

1 INTRODUCTION

Severe asthma is defined as asthma which requires treatment with high doses of inhaled corticosteroids plus a second controller and/or systemic corticosteroids to prevent it from becoming uncontrolled or which remains uncontrolled despite optimal therapy.1,2 Conversely, bronchiectasis is a pathologic description of lung damage characterised by inflamed and diluted thick-wall bronchi, with the classical symptoms of chronic cough and sputum production.3 The coexistence of bronchial asthma and bronchiectasis in many patients has generated the implication of a causative role of bronchial asthma in the development of bronchiectasis, but a clear aetiologic relation has not been precisely established.4 The imbalance between matrix metalloproteinases (MMPs) and tissue inhibitor of MMPs (TIMPs), which can lead to degradation of extracellular matrix, tissue destruction and subsequently to tissue remodelling, has received considerable

Clin Respir J. 2017;1–7. wileyonlinelibrary.com/journal/crj © 2017 John Wiley & Sons Ltd
attention as a mechanism of airway destruction and luminal dilatation in asthma that might potentially cause bronchiectasis. The persistent chronic inflammatory process is further aggravated by frequent exacerbations. A reduced phagocytic capacity of macrophages for bacteria has also been implicated in increased exacerbations, airway colonisation by bacteria and persistence of inflammation in airways of asthmatics. Indeed, bacterial colonisation of the lower airways is common in patients with chronic severe asthma, while it has been also found that sputum pathogens in severe asthma patients differ from healthy controls and nonsevere asthmatics.

The most common radiological features recognised in HRCT of asthmatics are bronchial wall thickening, bronchial dilation and air trapping. The presence of bronchiectasis in asthmatic patients varies from 3% to 80% in different reports.

In the present study, we intended to prospectively investigate the presence of bronchiectasis in a cohort of patients with severe asthma by HRCT of the chest and additionally examine whether the presence of bronchiectasis contributes to the severity of asthma.

2 MATERIAL AND METHODS

2.1 Study population

This study was approved by the Institutional Ethics Committee of ‘Sotiria’ Chest diseases hospital of Athens, Greece. Written informed consent was obtained from each patient. This is a cross sectional, uncenter study. We prospectively recruited patients examined at the outpatient pulmonary clinic over a period of two years (from 04/2013 until 05/2015) and fulfilled the criteria of severe asthma. After completion of the study all patients were reexamined as far as diagnosis was concerned based on the recently published ERS/ATS guidelines. All patients were found to fulfill the new criteria of severe uncontrolled asthma. Patients with a diagnosis of asthma-chronic obstructive pulmonary disease (COPD) overlap syndrome (ACOS) or a previously established diagnosis of bronchiectasis were excluded. All patients were free from asthma exacerbation for at least four weeks before entering the study. Exacerbations were defined as acute or subacute worsening in symptoms and lung function from the patient’s usual status. A complete medical history was taken and asthma characteristics were recorded. The asthma control test (ACT) was administered in order to estimate the control of asthma. The number of antibiotic and corticosteroid courses during the last year were recorded according to patients medical history and electronic files. Patients that were diagnosed with bronchiectasis underwent a thorough investigation in order to identify and exclude other possible aetiologies of bronchiectasis than asthma. This included a complete medical history and blood samples examination in order to measure levels of immunoglobulins (IgG, IgA, IgM) from all patients according to the BTS guideline on bronchiectasis. Total IgE, IgG and IgE antibodies against Aspergillus fumigatus and peripheral eosinophilia were measured in order to exclude allergic bronchopulmonary aspergillosis (ABPA). A sweat test or genotyping from blood sample and nasal NO measurement and/or brushing of nasal mucosa for electron microscopic analysis were performed in patients with a clinical and radiological presentation compatible with cystic fibrosis (CF) or primary ciliary dyskinesia, respectively. Alpha-1 antitrypsin was measured is patients with concomitant emphysema on the CT scans.

2.2 Radiology

All patients underwent a HRCT of the chest within two weeks from visit at the outpatient clinic. Images were obtained using 1-mm collimation at 10 mm intervals in full inspiration, interpreted by consensus of two thoracic radiologists who were unaware of clinical status. Bronchiectasis was diagnosed when a bronchus had an average internal diameter greater than 110% the accompanying pulmonary artery and failed to taper. According to its morphology bronchiectasis was categorised in cylindrical, varicose or cystic type. To estimate the extent of bronchiectasis a score was calculated in each lobe using the grading system proposed by Smith and coworkers as follows: 0 if no bronchiectasis was present; 1 if less than 25% of bronchi were bronchiectatic; 2 if 25–49% of the bronchi were bronchiectatic; 3 if 50–74% of the bronchi were bronchiectatic; and 4 if 75% or more of the bronchi were bronchiectatic. The lingula was graded as a separate lobe, resulting in a maximum score of 24 per patient. As previous studies have shown that more than 50% of healthy volunteers may have at least one dilated bronchus on HRCT, only patients with a total bronchiectasis score of 3 or more were considered to have clinically significant disease. Moreover, the Smith score was used as a quantitative variable for the whole group of patients in order to explore relationships with other variables.

2.3 Microbiology

Sputum samples were obtained in all patients for sputum cultures. In patients without expectoration induced sputum techniques were used. Only samples of Murray–Washington classification degrees IV and V were processed. A sputum sample from each patient was also stained with Ziehl–Nielsen and cultured with Lowenstein–Jensen for Mycobacteria.
Negative bacterial cultures were discarded after five days and Lowenstein cultures after eight weeks.

2.4 | Lung function

Forced expiratory volume in one second (FEV₁), forced vital capacity (FVC) and FEV₁/FVC ratio before and after bronchodilation were measured using Cosmed S.r.I. according to the American Thoracic Society guidelines. Measurements after bronchodilation were used for statistical analysis.

2.5 | Statistical analysis

For exploring the association between pairs of continuous variables a Pearson correlation analysis was applied. For the comparison of the groups of patients with or without bronchiectasis on various continuous variables a Mann–Whitney U test analysis was applied, due to the small and unequal sample size of the two groups. Also, a Mann–Whitney U test analysis was applied for comparing patients with and without sputum production as well as with and without a pathogen on various continuous variables. Finally, a chi-square test for independence analysis was applied for exploring the association between pairs of binary variables. Statistical significance was set at the .05 level. The Statistical Package for the Social Sciences (SPSS), version 21 (Chicago, ILL) was used to analyse the data.

3 | RESULTS

Forty patients with severe asthma were recruited with a mean age of 57.9 ± 12.4 years, most of them women (28 female, 12 male) and nonsmokers (32 nonsmokers, 6 smokers and 2 ex-smokers with a mean of 10 pack/year). None of the smokers or ex-smokers had fixed obstruction in spirometry. Demographic data and clinical, functional and microbiological profile are shown in Table 1. Mean ACT score was 14.2 ± 4.9 indicating uncontrolled asthma despite treatment. Main symptoms were cough, wheezing, chest tightness and dyspnea. Fourteen patients were atopic (35%). Eosinophilia in peripheral blood was found in nine patients (22.5%). All patients were treated with combination of inhaled corticosteroid (ICS)/long-acting beta2 agonist (LABA). Sixteen patients (40%) were also taking leukotriene receptor antagonist (LTRA). Twenty seven patients (67.5%) were diagnosed with bronchiectasis. Twenty three patients (85%) had cylindrical bronchiectasis, 4 patients (10%) had varicose bronchiectasis, while four patients (10%) had also cystic bronchiectasis in addition to cylindrical ones. In three patients a limited degree of emphysema was visible. After investigation no specific aetiologic cause of bronchiectasis occurred in any of the patients. Mean Smith score was 5.2 ± 2.2.

### TABLE 1  Demographic data and patients’ characteristics (n = 40)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/Female</td>
<td>12/28</td>
</tr>
<tr>
<td>Age (years, mean ± SD)</td>
<td>57.9 ± 12.4 (range 30–83)</td>
</tr>
<tr>
<td>Smokers/nonsmokers/ex-smokers</td>
<td>6/32/2</td>
</tr>
<tr>
<td>Asthma characteristics</td>
<td></td>
</tr>
<tr>
<td>Years of asthma diagnosis (mean ± SD)</td>
<td>16.5 ± 11.5</td>
</tr>
<tr>
<td>ACT (mean ± SD)</td>
<td>14.2 ± 4.9</td>
</tr>
<tr>
<td>Allergic rhinitis (yes/no)</td>
<td></td>
</tr>
<tr>
<td>Sinusitis (yes/no)</td>
<td></td>
</tr>
<tr>
<td>Cough (yes/no)</td>
<td></td>
</tr>
<tr>
<td>Wheezing (yes/no)</td>
<td></td>
</tr>
<tr>
<td>Dyspnea (yes/no)</td>
<td></td>
</tr>
<tr>
<td>Chest tightness (yes/no)</td>
<td></td>
</tr>
<tr>
<td>Exacerbations/year (mean ± SD)</td>
<td>4.4 ± 2.7</td>
</tr>
<tr>
<td>Corticosteroid cycles/year (mean ± SD)</td>
<td>4.4 ± 3.1</td>
</tr>
<tr>
<td>Antibiotic cycles/year (mean ± SD)</td>
<td>2.8 ± 3.2</td>
</tr>
<tr>
<td>Bronchiectasis in HRCT (yes/no)</td>
<td>27/13</td>
</tr>
<tr>
<td>Smith score of bronchiectasis (mean ± SD)</td>
<td>5.2 ± 4.2</td>
</tr>
<tr>
<td>FEV₁ % post (mean ± SD)</td>
<td>72.6 ± 21.1</td>
</tr>
<tr>
<td>FVC % post (mean ± SD)</td>
<td>79.1 ± 19.4</td>
</tr>
<tr>
<td>FEV₁/FVC post (mean ± SD)</td>
<td>67.3 ± 9.7</td>
</tr>
<tr>
<td>Sputum production (yes/no)</td>
<td>29/11</td>
</tr>
<tr>
<td>Mucoid (n)</td>
<td>15</td>
</tr>
<tr>
<td>Mucopurulent (n)</td>
<td>12</td>
</tr>
<tr>
<td>Purulent (n)</td>
<td>2</td>
</tr>
</tbody>
</table>

| Sputum culture (n = 40)         |               |
| Normal flora/pathogens          | 31 (77.5%)/9 (22.5%) |
| *P. aeruginosa*                 | 1             |
| *P. aeruginosa*+other pathogen  | 5             |
| Other pathogen*                 | 3             |

FEV₁%, FVC%, FEV₁/FVC post: postbronchodilation values. Patients without sputum production were presumed to have negative sputum cultures.

H. influenzae, six patients, Klebsiella pneumoniae, two patients, Streptococcus pneumoniae, two patients, Acinetobacter baumannii, one patient.

4.2 for all patients, 7.3 ± 3.4 for the 27 bronchiectatic patients and .84 ± .8 for the group of patients without bronchiectasis. In 9 (22.5%) patients one or more pathogens were identified in sputum cultures, the most frequent of which were *P. aeruginosa* and *H. influenza* (Table 1). All patients that had pathogens in sputum cultures were diagnosed with bronchiectasis. Patients with bronchiectasis consumed more antibiotics (courses per year) compared to patients without bronchiectasis (3.56 ± 2.3 vs 1.46 ± 1, respectively, Z = 2.8, P = .004) (Figure 1). Between these two groups of patients no other statistically significant differences were noticed. The Smith score was significantly correlated with the antibiotic courses/year (r = 0.48, P = .002) (Figure 2). Patients with sputum production had a higher Smith score in relation to those without expectoration (6.3 ± 4.2 vs 2.3 ± 2.2,
respectively, \( Z = 2.8, P = .005 \). In addition, patients with pathogens in sputum cultures had a higher Smith score and a higher number of antibiotic courses/year compared to patients without pathogens (10 \( \pm \) 4.2 vs 3.8 \( \pm \) 3, \( Z = 3.5, P < .0001 \) for Smith score, 5 \( \pm \) 1.9 vs 2.2 \( \pm \) 1.9, \( Z = 3.3, P = .001 \) for antibiotic courses/year, respectively) (Figure 3A,B). When patients were divided in groups according to their sputum quality, it was found that patients with mucopurulent or purulent sputum (\( n = 14 \)) had consumed more antibiotics during the last year than patients with production of mucoid sputum (\( n = 15 \)) (4.5 \( \pm \) 2.6 antibiotic courses/year vs 2.2 \( \pm \) 0.9, \( Z = 2.5, P = .01 \)) (Figure 4). Finally, a lower ACT score was related with a higher exacerbation rate (\( r = -0.52, P = .001 \)) and more corticosteroid courses/year (\( r = -0.45, P = .005 \)), but was not found to correlate with any parameter from the lung function tests.

4 | DISCUSSION

We prospectively studied a cohort of severe asthmatic patients for the presence of bronchiectasis by HRCT of the chest using the ‘Smith’ grading system and identified a high frequency of bronchiectasis in patients with severe asthma. In addition, asthmatics with bronchiectasis were more
frequently colonised with pathogens and more frequently used antibiotics, while more extensive radiological disease was related with a greater use of antibiotics.

Structural changes are common in HRCT of patients with asthma, especially for those with more severe disease, as bronchial wall thickness and air trapping have been described in approximately 80% of patients with moderate-to-severe asthma.\textsuperscript{18,19} Indeed, a HRCT of the chest is not suggested among the investigation of severe asthma, but it is preserved only for cases of atypical presentation of severe asthma.\textsuperscript{1,2} Cylindrical bronchiectasis can be seen in 17–20% of patients with mild asthma, while the prevalence of bronchiectasis in severe asthmatics is more evident, though data on severe asthma population are limited.\textsuperscript{10,12,20} In a study evaluating the prevalence of bronchiectasis in asthma according to oral steroid requirement, bronchiectasis was found in 20% in the steroid depended group and only 4% in the nonsteroid depended group.\textsuperscript{21} Oguzuglen and coworkers, in a study of 1680 asthmatic patients, found that 3% of patients had radiographically evident bronchiectasis, and around 50% of patients with bronchiectasis had severe asthma.\textsuperscript{13} However, other causes of bronchiectasis were not investigated. In a large cross-sectional retrospective analysis of patients with severe asthma, bronchiectasis was present in 40% of cases.\textsuperscript{22} Nevertheless, the high prevalence of bronchiectasis in this cohort of patients can be interpreted by the fact that for the majority of patients the most common indication for HRCT was a clinical suspicion of bronchiectasis. Conversely, bronchial asthma is increasingly and clearly recognised as a causative factor of bronchiectasis.\textsuperscript{4} The high frequency of bronchiectasis in this patient group is probably attributed to the careful selection criteria of severe asthma for inclusion in the study and its prospective nature that allowed the screening for bronchiectasis to be performed in one medical center and interpreted by special thoracic radiologists. Finally, the rather long duration since asthma diagnosis may have contributed to the high prevalence of bronchiectasis among this cohort of patients, since bronchiectasis as a consequence of asthma need time to develop.

The Smith score of bronchiectasis was initially used in the investigation of bronchiectasis on HRCT in patients who presented with chronic sputum production.\textsuperscript{15} There are recent data that propose new methods which could objectively identify and quantify bronchiectasis, such as quantitative computed tomography measures of bronchial lumen and adjacent artery ratios, but these methods are not yet examined in large series.\textsuperscript{25} However, the Smith score has been found to correlate with dyspnea from the clinical characteristics and the FEV\textsubscript{1} % from the functional parameters.\textsuperscript{15} In asthma studies, several radiological scales have shown conflicting data concerning the correlation of bronchiectasis with the parameters of PFT.\textsuperscript{8,9,16,26} In the present study, no correlation was found between pulmonary function test parameters and either the presence of bronchiectasis or the quantitative measurement with the Smith scale as well. We believe that the differences in the reported results could be due to the different populations of asthma severity studied, the various criteria used to define asthma severity and the differences in radiological devices used to measure and grade CT alterations. Indeed, several studies have indicated that bronchiectasis are mainly characterised by airflow obstruction, which may arise primarily from inflammation in small airways.\textsuperscript{27,28} In addition, FEV\textsubscript{1} is widely accepted as a good predictor of morbidity and mortality in bronchiectasis patients.\textsuperscript{29,30} Therefore, the severity of asthma in cases of coexistence of asthma and bronchiectasis may result from the presence of bronchiectasis and its impact on the clinical features of asthma and this could partially explain the absence of correlation between PFTs and ‘Smith’ scale.

Regarding the relationship between bronchiectasis in this cohort of severe asthma patients and other clinical features, we found that the Smith score was significantly correlated with the antibiotic consumption, sputum production and the presence of pathogens in sputum cultures. This finding could denote the fact that in patients with severe asthma and bronchiectasis, the clinical characteristics of bronchiectasis may the predominant features. In fact, bronchial colonisation by pathogenic microorganisms is common in bronchiectatic patients and in particular, colonisation by \textit{P. aeruginosa} has been documented as an independent predictor of mortality.\textsuperscript{31} However, little information exists about bronchial colonisation in severe asthma. In a previous study concerning patients with stable severe asthma, bacterial colonisation of the lower airways was common and was linked to the duration of asthma and the number of exacerbations in the past year, but not with an increase in airway wall thickness in CT, a marker of asthma severity and airflow obstruction.\textsuperscript{6,32} In the present study a significant number of patients were colonised with pathogens (22.5%) and of note 15% of them with \textit{P. aeruginosa}. All of them had bronchiectasis and also had more extensive radiological disease than those without pathogens in sputum cultures.

There are important therapeutic implications to identifying bronchiectasis in patients with severe asthma. Bronchiectasis is considered to be a neutrophilic airway disease, while neutrophilic asthma is considered to be a small subgroup of patients with asthma.\textsuperscript{33} While eosinophilic inflammation is corticosteroid responsive, the same is not true for
neutrophilic airway inflammation. Studies in bronchiectasis show that macrolide antibiotics reduce the frequency of exacerbations and studies in asthma have suggested that macrolides can reduce exacerbations in the subgroup with neutrophilic asthma.\textsuperscript{34,35} ICSs in contrast are the mainstay of treatment in asthma but have no evidence to support their use in bronchiectasis.\textsuperscript{36} Therefore, important questions arising from our work include whether macrolides may be more effective than corticosteroids in the group of patients with severe asthma and bronchiectasis and whether the reason for the preponderance of bronchiectasis patients in the severe asthma cohort reflects a selection of a subgroup of patients, or a ‘phenotype’ that is nonresponsive to inhaled steroids due to neutrophilic airway inflammation.

The main limitation of this study is the rather small number of patients included that did not allow an analysis according to pathogenic microorganisms in sputum of severe asthmatics with radiological indices. However, this was a prospective analysis of a well selected group of severe asthmatic patients, and importantly in patients diagnosed with bronchiectasis, a rigorous investigation and exclusion of other possible causes of bronchiectasis was carried out.

In conclusion, the high percentage of bronchiectasis found in patients with severe uncontrolled asthma, justifies the need for further investigation of this group of patients with HRCT of the chest. Moreover, it seems that the bronchiectatic clinical features are the predominant for this group and are the only to correlate with bronchiectasis radiological score. Finally, the presence of bronchiectasis seems to contribute to the severity of asthma.

**CONFLICT OF INTERESTS**

All authors declare that they have no conflicts of interest.

**AUTHOR CONTRIBUTIONS**

*Designed research/study:* Dimakou

*Performed research/study:* Dimakou, Thanos, Triantafillidou

*Analysed data:* Gousiou

*Collected data:* Toumbis, Kaponi, Chrysikos, Triantafillidou

*Wrote the paper:* Dimakou, Triantafillidou

**ETHICS**

This study was approved by the Institutional Ethics Committee of ‘Sotiria’ Chest diseases hospital of Athens, Greece. Written informed consent was obtained from each patient.

**REFERENCES**


19. Awadh N, Müller NL, Park CN, Abboud RT, FitzGerald JM. Airway wall thickness in patients with near fatal asthma and


