



Bronchiectasis in severe asthma Clinical features and outcomes

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ABSTRACT

Background: Bronchiectasis is increasingly being identified in patients with severe asthma and could contribute to disease severity.

Objective: To determine the prevalence of bronchiectasis in a population of patients with severe asthma and to better characterize the clinical features of these patients and their outcomes.

Methods: We retrospectively reviewed the medical files of 184 subjects with confirmed severe asthma who had undergone high-resolution thoracic computed tomography and compared the characteristics and outcomes of subjects with and without bronchiectasis.

Results: Bronchiectasis was identified in 86 patients (47%). These patients had concomitant hypersensitivity to nonsteroidal anti-inflammatory drugs (odds ratio [OR] 2.24, 95% confidence interval [CI] 1.00–5.03) and gastroesophageal reflux disease (OR 1.89, 95% CI 1.05–3.41) more frequently than subjects without bronchiectasis, but had less atopic dermatitis (OR 0.188, 95% CI 0.04–0.88). Subjects with bronchiectasis were more frequently hospitalized for asthma exacerbations (OR 2.09, 95% CI 1.08–4.05) and had higher blood eosinophil levels (464 vs 338; $P = .005$) than subjects without bronchiectasis.

Conclusion: Our study suggests that in subjects with severe asthma, the presence of bronchiectasis is associated with more frequent hospitalizations, concomitant gastroesophageal reflux disease, hypersensitivity to nonsteroidal anti-inflammatory drugs, and higher blood eosinophil counts. Bronchiectasis could represent an additional phenotypic feature of severe eosinophilic asthma.

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Introduction

Despite a prevalence of 5% to 10% of all asthma cases, severe asthma disproportionately contributes to asthma-related health care costs.^{1,2} The investigation and treatment of comorbidities are of major importance in patients with severe asthma, because they contribute to poor disease control.

Bronchiectasis is defined radiologically as focal or diffuse irreversible dilation of the airways and results from loss of elastin, muscle, and cartilage, with variable fibrosis of bronchial walls and peribronchial changes.³ Some groups have described bronchiectasis as a comorbidity associated with asthma,⁴ whereas others have identified asthma as being one of many etiologies of bronchiectasis.^{5–7} The presence of bronchiectasis has been reported

in 17.5% to 80% of asthma cases,^{8–10} and asthma severity and bronchiectasis have been linked to atopy¹¹ and sensitization to fungi such as *Alternaria*, *Cladosporium*, and *Aspergillus* species.^{12,13}

In this study, we aimed to retrospectively determine the prevalence of bronchiectasis in our population of patients with severe asthma and to describe the characteristics and outcomes of these patients in exacerbation rates and hospitalizations. Furthermore, because sensitization to fungi is associated with poor asthma control and disease complications, we hypothesized that the prevalence of fungal sensitization in patients with bronchiectasis would be higher than in patients without bronchiectasis.

Methods

Subjects

We retrospectively collected data from patients referred for evaluation of severe or uncontrolled asthma to the Severe Asthma Clinic of Hospital Universitario La Paz (Madrid, Spain) from 2010 through

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2013. Severe asthma was defined according to the European Respiratory Society and American Thoracic Society Taskforce on Severe Asthma¹; asthma required Global Initiative for Asthma step 4 or 5 treatment (ie, high-dose inhaled corticosteroid with a long-acting β -agonist or leukotriene modifier or theophylline) or systemic corticosteroid use at least 50% of the previous year to maintain control or remained “uncontrolled” despite this treatment.¹ The diagnosis was objectively confirmed in all patients by bronchodilator response testing or a positive methacholine bronchial provocation test reaction.¹⁴ Once the diagnosis was confirmed, additional standard investigations were performed in all patients with severe asthma. Sensitization to common aeroallergens including local pollens (*Cupressus arizonica*, *Platanus acerifolia*, *Olea europaea*, Gramineae mix, *Artemisia vulgaris*), dust mites (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Lepidoglyphus destructor*), cockroach, fungi (*Aspergillus fumigatus*, *Alternaria alternata*, *Cladosporium herbarum*), and cat and dog dander were determined by skin prick testing and specific immunoglobulin E (IgE) levels. Skin prick test results were considered positive when eliciting a wheal diameter of at least 3 mm compared with negative (saline) and positive (10 mg/mL of histamine) controls for interpretation.¹⁵ Measurement of total serum IgE levels and specific IgE levels for aeroallergens and fungi (*A fumigatus*, *A alternata*, *C herbarum*, *Candida albicans*) were performed in all patients using a commercial ImmunoCAP kit (ThermoFisher Scientific, Uppsala, Sweden). Atopy was defined as the presence of at least 1 positive skin prick test or specific serum IgE reaction. Basic hematology and serum levels of eosinophilic cationic protein and serum antineutrophilic cytoplasmic antibody levels also were performed in all patients, as was high-resolution computed tomographic densitography (HRCT) of the thorax. Additional investigations such as sinus CT, sweat test, and pH-metry were performed as needed on a per-patient basis. Alternative diagnoses such as, but not limited to, smoking-related chronic obstructive pulmonary disease, allergic bronchopulmonary mycosis, eosinophilic granulomatosis with polyangiitis, and cystic fibrosis were investigated and excluded based on clinical suspicion and investigation results. We included patients referred for uncontrolled or severe confirmed asthma who completed these investigations. The institutional ethics committee of the hospital approved the study and the use of confidential data.

Bronchiectasis on HRCT

Standard criteria for bronchiectasis diagnosis on thoracic HRCT complied with the Spanish Society of Pneumology and Thoracic Surgery recommendations and were the identification of a bronchus with an internal diameter larger than that of its accompanying vessel or the absence of bronchus tapering in the periphery of the lungs.¹⁶ Most HRCTs were performed in the context of the asthma investigation, unless results were available from an HRCT performed within the past 6 months.

Statistical Analysis

Demographic, clinical, and functional information was collected from the medical history and electronic files of all included patients. Statistical analysis was performed with IBM SPSS Statistics 25 (IBM Corp, Armonk, New York). Values were expressed as mean $\pm$ SD. Continuous variables were compared using the Student *t* test, and the χ^2 or Fisher exact test was used to compare categorical variables. All *P* values are taken from 2-tailed tests and values less than .05 were considered statistically significant. Logical regression analyses were performed using 95% confidence intervals (CIs).

Results

A total of 264 patients were referred for evaluation of severe asthma. After the exclusion of 80 subjects who did not have thoracic HRCT results or interpretation, data from 184 patients were analyzed.

Demographic, clinical, and functional data according to the presence or absence of bronchiectasis are presented in Table 1. More than 90% of patients were on Global Initiative for Asthma treatment steps 4 and 5. Of the 184 patients, 86 (47%) had bronchiectasis. These subjects were on average older than those without bronchiectasis. Patients with bronchiectasis had a concomitant diagnosis of intolerance to nonsteroidal anti-inflammatory drugs (NSAIDs; 22% vs 11%; *P* = .046, odds ratio [OR] 2.24, 95% CI 1.00–5.03) and gastroesophageal reflux disease (GERD; 62% vs 46%; *P* = .033, OR 1.89, 95% CI 1.05–3.41) more frequently than those without bronchiectasis. Atopic dermatitis was less frequently documented in subjects with bronchiectasis (2% vs 11%; *P* = .019, OR 0.188, 95% CI 0.04–0.88).

There was no difference in common aeroallergen and fungal sensitization, because 22% of subjects in each group were sensitized to any of 4 fungi (*A fumigatus*, *A alternata*, *C herbarum*, *C albicans*). Subjects with bronchiectasis had significantly higher blood eosinophil levels (464 vs 338; *P* = .005) and higher serum eosinophil cationic protein levels (58 vs 43; *P* = .003) than subjects without bronchiectasis but had comparable IgE levels (*P* 0.65). There was no significant difference in maintenance treatment between groups.

In the year before evaluation in our service, 83 subjects (97%) with bronchiectasis and 88 subjects (90%) without bronchiectasis presented at least 1 asthma exacerbation, with similar exacerbation averages in the 2 groups (3.45 vs 3.39; *P* = .09, OR 3.14, 95% CI 0.84–11.82). More patients with bronchiectasis were hospitalized for an asthma exacerbation in the year before the consultation in our service compared with patients without bronchiectasis (35% vs 20%; *P* = .028, OR 2.09, 95% CI 1.08–4.05). The association remained significant when adjusted (Table 2) for the presence of GERD and intolerance to NSAIDs in multiple logistical regression analysis (OR 2.02, 95% CI 1.03–3.98). When specifically looking at subjects on maintenance oral corticosteroids, there was no difference in exacerbations, hospitalizations, blood eosinophil counts, or eosinophilic cationic protein between subjects with and without bronchiectasis.

Discussion

Bronchiectasis is a frequent finding that affected half the subjects with severe asthma in our population. Patients with coexistent severe asthma and bronchiectasis are twice as likely to be hospitalized for asthma exacerbations as patients with severe asthma alone, and the coexistence of the 2 conditions is associated with hypersensitivity to NSAIDs, GERD, and higher blood eosinophil counts.

At least 1 abnormality was detected by thorax HRCT in up to 85% of subjects with asthma; the most commonly reported were trapped air, bronchial wall thickening, and bronchial dilation.^{17,18} The prevalence of bronchiectasis in patients with any severity of asthma is generally low, increases considerably in patients with severe asthma (25%–51%),^{4,17} and is generally correlated to asthma severity,^{16,19} as in the present study. The coexistence of these 2 pathologies has been associated with an increased risk of exacerbation, hospitalization, and chronic respiratory failure.^{20,21} One group reported that half their patients with coexistent asthma and bronchiectasis had been hospitalized for an asthma exacerbation at least once in their lifetime compared with 17.6% of patients with asthma alone.¹⁹ Our study exclusively collected data on events that occurred the year before the patients' evaluation in our unit. Although exacerbation rates were

Table 1
Demographic Characteristics

Patient characteristic	Asthma with bronchiectasis (n = 86, 47%)	Asthma without bronchiectasis (n = 98, 53%)	P value ^a
Age, average (SD)	56 (16.49)	48 (13.12)	.003
Sex, n (%)	67 (78)	78 (78)	.954
Smoker, n (%)	45 (52)	46 (47)	.466
GINA treatment step, n (%)			
Step 3	5 (6)	12 (12)	.133
Step 4	59 (69)	55 (56)	.082
Step 5	22 (26)	31 (32)	.366
Oral anti-leukotriene, n (%)	50 (58)	56 (57)	.678
Inhaled anticholinergic, n (%)	46 (53)	45 (46)	.305
Oral azithromycin, n (%)	3 (3)	0 (0)	.082
Oral corticosteroids, n (%)	25 (29)	28 (29)	.941
Omalizumab, n (%)	14 (16)	12 (12)	.433
FEV ₁ %, average (SD)	76 (23.45)	82 (23.99)	.972
FEV ₁ /FVC %, average (SD)	66 (13.40)	71 (15.48)	.584
Atopy, n (%)	51 (59)	61 (62)	.683
Allergic rhinitis, n (%)	46 (53)	27 (28)	.230
Chronic rhinosinusitis, n (%)	31 (36)	27 (28)	.216
Atopic dermatitis, n (%)	2 (2)	11 (11)	.019
NSAID hypersensitivity, n (%)	19 (22)	11 (11)	.046
Gastroesophageal reflux disease, n (%)	53 (62)	45 (46)	.033
Total serum IgE, average (SD)	383 (600)	356 (821)	.65
Blood eosinophils/μL, average	464 (445)	338 (260)	.005
Eosinophil cationic protein, average (SD)	58 (47)	43 (35)	.003
Sensitizations (skin prick), n (%)			
<i>Cupressus arizonica</i>	20 (23)	25 (26)	.723
<i>Platanus acerifolia</i>	8 (9)	18 (18)	.078
<i>Olea europaea</i>	22 (26)	27 (28)	.763
Gramineae	28 (33)	43 (44)	.116
<i>Artemisia vulgaris</i>	6 (7)	8 (8)	.762
<i>Chenopodium album</i>	13 (15)	20 (20)	.351
<i>Dermatophagoides pteronyssinus</i>	5 (6)	14 (14)	.060
<i>Dermatophagoides farinae</i>	8 (9)	15 (15)	.219
<i>Lepidoglyphus destructor</i>	10 (12)	9 (9)	.587
Cockroach	3 (3)	1 (1)	.252
<i>Alternaria alternata</i>	2 (2)	6 (6)	.208
<i>Aspergillus fumigatus</i>	7 (8)	8 (8)	.995
<i>Cladosporium herbarum</i>	1 (1)	3 (3)	.378
Cat dander	13 (15)	28 (23)	.154
Dog dander	23 (23)	26 (27)	.350
Sensitizations (serum IgE), n (%)			
<i>Candida albicans</i>	7 (8)	13 (13)	.268
<i>Aspergillus fumigatus</i>	15 (17)	11 (11)	.229
Sensitization (prick reaction or IgE) to ≥1 fungus, n (%)	19 (22)	22 (22)	.954
Had ≥1 exacerbation/y, n (%)	83 (97)	88 (90)	.076
Exacerbations/y, average (SD)	3.45 (2.21)	3.39 (2.73)	.090
Had ≥1 hospitalization/y, n (%)	30 (35)	20 (20)	.028
Hospitalizations/y, average (SD)	0.56 (0.94)	0.31 (0.71)	.004

Abbreviations: FEV₁, forced expiration volume in 1 second; FVC, forced vital capacity; GINA, Global Initiative for Asthma; IgE, immunoglobulin E; NSAID, nonsteroidal anti-inflammatory drug.

^aSignificant at less than .05.

Table 2
Predictors of Bronchiectasis in Subjects With Severe Asthma

Predictor	OR	95% CI
Atopy	0.884	0.488–1.600
Allergic rhinitis	0.698	0.387–1.256
Rhinosinusitis	1.482	0.794–2.768
Atopic dermatitis	0.188	0.041–0.875
Hypersensitivity to nonsteroidal anti-inflammatory drugs	2.243	1.000–5.032
Gastroesophageal reflux disease	1.892	1.050–3.408

Abbreviations: CI, confidence interval; OR, odds ratio.

similar, 35% of subjects with bronchiectasis had been hospitalized at least once compared with 20% of subjects without bronchiectasis ($P = .028$).

The reported prevalence of asthma in subjects with bronchiectasis ranges from 2.7% to 40%.^{19,22} The 2017 US Bronchiectasis

Research Registry²³ reported a clinical diagnosis of asthma in 29% of patients, but fewer than 5% of patients had confirmed asthma. In fact, in recent cohort studies, asthma was identified as the etiology of bronchiectasis in only 3% to 5.4% of cases,^{6,24} and the British Thoracic Society non-cystic fibrosis bronchiectasis guidelines⁷ suggest the consideration of asthma as the etiology of bronchiectasis in the absence of other causes. Asthma was the etiology of bronchiectasis in 5.4% of 2,047 patients in a Spanish Registry Study and was correlated to poorer lung function but less chronic bronchial infection.²⁵ The incidence of exacerbations in patients with asthma and bronchiectasis is high, with patients being 1.6 to 2.6 times as likely to present an exacerbation as patients without bronchiectasis.²⁶ This suggests that the coexistence of these 2 pathologies worsens outcomes, as in the present study.

Our results associated the presence of bronchiectasis with the coexistence of hypersensitivity to NSAIDs and GERD, 2 important comorbidities of asthma. The prevalence of aspirin-exacerbated respiratory disease in severe asthma is 15%²⁷ and is strongly associated

with exacerbations,²⁸ but it has not been associated with bronchiectasis in the current literature. In contrast, the reported prevalence of GERD in asthma is 35%–82%²⁹ (and 26%–75%^{4,22} in bronchiectasis), and it has been associated with poor disease control and increased risk of exacerbation for the 2 pathologies.^{30,31} However, there are limited data on the effects of treating GERD in patients with asthma³² or bronchiectasis³³ because most studies have significant limitations and report divergent results.

Although early studies documented a relation among asthma, bronchiectasis, and atopy,^{34,35} many others did not,^{19,21} even when specifically looking at subjects with severe asthma as in the present study. Likewise, some studies have documented an association between bronchiectasis and fungi-sensitized asthma.³⁶ However, compared with our study, patients with allergic bronchopulmonary mycosis are always not systematically excluded from analyses of bronchiectasis and fungal sensitization in asthma.³⁷ Because the criteria used for allergic bronchopulmonary mycosis vary greatly, these patients also might be mislabeled as having severe asthma with fungal sensitization. This could explain why we did not observe an association between fungal sensitization and bronchiectasis in our patients. In contrast, the lower incidence of atopic dermatitis in subjects with bronchiectasis, in the context of comparable levels of total serum IgE levels, could be hypothetically explained by factors such as fungal colonization.³⁸ In atopic dermatitis, a T-helper cell type 2 response is developed against common allergens, which in turn promotes IgE secretion by plasma cells. However, in patients with asthma and bronchiectasis, in the absence of other criteria of allergic bronchopulmonary aspergillosis, the increased secretion of IgE could be driven by other factors such as fungal colonization and infection,³⁹ which have previously been associated with increased total serum IgE levels.

It is difficult to determine whether the severity of asthma in subjects with coexistent bronchiectasis is due to the presence of bronchiectasis or whether the presence of bronchiectasis is a manifestation of asthma severity. The higher levels of blood eosinophils and eosinophil cationic protein we observed in patients with coexistent bronchiectasis (464 vs 338, $P = .005$; and 58 vs 43, $P = .003$, respectively) seem to suggest the latter. Induced sputum was not systematically performed in our population, but there is a strong correlation between sputum and blood eosinophil levels in patients with asthma.⁴⁰ Our findings suggest that the presence of bronchiectasis could be another criterion to identify patients with severe eosinophilic asthma (SEA), thus identifying a subset of patients among those with SEA.⁴¹

Macrolides have been proved to lower exacerbation rates in subjects with asthma and subjects with non-cystic fibrosis bronchiectasis,^{42,43} often at the cost of increased antimicrobial resistance. In the recent AMAZES⁴⁴ trial, regular treatment with azithromycin decreased the rate of severe exacerbations requiring treatment with systemic corticosteroids or hospitalization (incidence rate ratio 0.59, 95% CI 0.42–0.83) in subjects with moderate to severe asthma. Although there were only 3 patients on long-term azithromycin treatment in our study, the addition of azithromycin to current treatment regimens could prove beneficial in this population.

The large number of patients and the systematic investigations performed in all patients evaluated in the multidisciplinary severe asthma unit are important strengths of the present study. The limitations are mainly related to its retrospective design. The bronchiectasis documented by HRCT was not classified or scored according to severity and was included in the analysis, whether or not it was clinically significant. However, had only clinically significant bronchiectasis been considered, it would likely strengthen the associations found in our study. Although recall bias could underestimate the exacerbation and hospitalization rates, this would be expected to affect the 2 groups.

Bronchiectasis was identified in half our population of subjects with severe asthma and is independently associated with an increased risk of hospitalization. Our study suggests an association among bronchiectasis, concomitant GERD, and hypersensitivity to NSAIDs, a finding that deserves further exploration. These patients also present higher serum eosinophil counts than comparable subjects without bronchiectasis and could represent a phenotype within SEA. The extent of the immunopathologic roles of the eosinophil in SEA has yet to be fully understood, and prospective studies on routine HRCT and active treatment of bronchiectasis in subjects with severe asthma are needed to help guide management in this population.

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