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Does asthma-bronchiectasis overlap syndrome (ABOS) really exist?

Angelica Tiotiu, MD, PhD[a,b], Miguel-Angel Martinez-Garcia, MD, PhD[c,d], Paula Mendez-Brea, MD[e], Iria Roibas-Veiga, MD[e] and Francisco-Javier Gonzalez-Barcala, MD, PhD[d,f,g,h]

[a]Department of Pulmonology, University Hospital of Nancy, Nancy, France; [b]Development, Adaptation and Disadvantage, Cardiorespiratory Regulations and Motor Control (EA 3450 DevAH), University of Lorraine, Nancy, France; [c]Respiratory Department, Hospital Universitario y Politécnico La Fe, Valencia, Spain; [d]Centro de Investigación Biomédica en Red (CIBERES), Instituto de Salud Carlos III, Madrid, Spain; [e]Allergy Department, Complejo Hospitalario Universitario de Santiago de Compostela, Santiago de Compostela, Spain; [f]Traslational Research In Airway Diseases (TRIAD)-Fundación Instituto de Investigación Sanitaria de Santiago de Compostela (FIDIS), Santiago de Compostela, Spain; [g]CIBER of Respiratory Diseases-CIBERES, Madrid, Spain; [h]Respiratory Department, Complejo Hospitalario Universitario de Santiago de Compostela, Santiago de Compostela, Spain

ABSTRACT

Objective: To analyze the relationship between asthma and bronchiectasis, as well as the necessary conditions that this connection must meet for this group of patients to be considered a special phenotype.

Data sources: We performed a PubMed search using the MeSH terms "asthma" and "bronchiectasis." The literature research was limited to clinical trials, meta-analyses, randomized controlled trials, cohort studies, and systematic reviews, involving adult patients, published until November 30th, 2022.

Study selections: Selected papers were initially evaluated by the Authors, to assess their eligibility in contributing to the statements.

Results: The prevalence of bronchiectasis is higher than expected in patients with asthma, particularly in those with more severe disease, and in some patients, between 1.4% and 7% of them, asthma alone could be the cause of bronchiectasis. Both diseases share etiopathogenic mechanisms, such as neutrophilic and eosinophilic inflammation, altered airway microbiota, mucus hypersecretion, allergen sensitization, immune dysfunction, altered microRNA, dysfunctional neutrophilic activity, and variants of the HLA system. Besides that, they also share comorbidities, such as gastroesophageal reflux disease and psychiatric illnesses. The clinical presentation of asthma is very similar to patients with bronchiectasis, which could cause mistakes with diagnoses and delays in being prescribed the correct treatment. The coexistence of asthma and bronchiectasis also poses difficulties for the therapeutic focus.

Conclusions: The evidence available seems to support that the asthma-bronchiectasis phenotype really exists although longitudinal studies which consistently demonstrate that asthma is the cause of bronchiectasis are still lacking.

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1. Introduction

Asthma is a chronic inflammatory disease that can be defined as having properties such as shortness of breath, wheezing, chest tightness, and coughing as well as variable expiratory airflow limitation, affecting between 1% and 18% of the world's population (1). It creates a high financial and social impact in both direct and indirect costs, particularly in cases of severe asthma (1–5). In the last few years, it has become clearer that asthma significantly affects the elderly, with a similar prevalence to that of young adults (6).

Bronchiectasis is usually defined as a chronic airway disease characterized by permanent bronchial dilatations and recurrent symptoms such as coughing, expectoration, and recurrent respiratory infections (7). Although historically, bronchiectasis has been considered an orphan disease, it is the third most common airway disease. The estimated prevalence of bronchiectasis ranges from 42 to 566 cases per 100 000 inhabitants, mainly women and the elderly being most affected (8,9). Many studies have shown a clear upward trend in bronchiectasis prevalence. For instance, it was a 40% increase in the United Kingdom between 2004 and 2014, and 55% in Germany between

CONTACT Francisco-Javier Gonzalez-Barcala francisco.javier.gonzalez.barcala@sergas.es Traslational Research in Airway Diseases (TRIAD)-Fundación Instituto de Investigación Sanitaria de Santiago de Compostela (FIDIS), C/Choupana SN. 15706, Santiago de Compostela, Spain.

2009 and 2017 (10,11). Likewise, it has a high mortality, more than twice as much as the general population. In a study carried out in two Spanish hospitals, it has been observed that there is a 12.5% mortality per year (12).

The increase in prevalence may be for many reasons. The more frequent use of CT scans, professionals being made more aware of the illness existing, the realization that it overlaps with other illnesses such as asthma, and the aging of the population due to bronchiectasis prevalence increasing with age might be some of the reasons behind this increase in prevalence (8,10).

Given the high prevalence of both asthma and bronchiectasis, it can be expected for them to coincide in the same patient in theory without there being any link between either of them. However, lately, some studies have observed that asthma and bronchiectasis may be related in different ways and even conform to a special group of patients with a specific treatment (phenotype) and physiopathological base (endotype). In this review, the available scientific evidence of the relationship between asthma and bronchiectasis will be presented as well as the necessary conditions that this connection must meet for this group of patients to be considered a special phenotype of patients.

1.1. Data sources

We performed a PubMed search using the MeSH terms "asthma" and "bronchiectasis." The literature research was limited to clinical trials, meta-analyses, randomized controlled trials, cohort studies, and systematic reviews, involving adult patients, published until November 30th, 2022.

1.2. Study selections

Selected papers were initially evaluated by the authors of the article, all of them respiratory or allergy specialist doctors, to assess their eligibility in contributing to the statements. In December 2022, the draft of the article was circulated among the Authors who appraised, discussed, modified, and approved the final version.

2. Clinical phenotype: necessary conditions

Even though there is no agreed definition of clinical phenotype, some authors have considered that it refers to a homogenous group of patients, within the heterogeneity of a specific illness, whether it be in its clinical picture, prognosis, or response to treatment. Others, however, have proposed a stricter definition, believing that in order to test for the existence of a phenotype, a physiopathological relationship should be established among the illnesses that shape it. We adopted the stricter definition for this review, which will attempt to respond to the question as regards whether asthma and bronchiectasis form a characteristic phenotype of patients, six conditions will be analyzed: (1) Biological plausibility; (2) prevalence of bronchiectasis in asthma; (3) impact of bronchiectasis on clinical outcomes; (4) impact of bronchiectasis on asthma prognosis; (5) impact of bronchiectasis on asthma treatment and (6) asthma-bronchiectasis endotype.

3. Biological plausibility

For now, there are no longitudinal studies available that consistently demonstrate that asthma is the cause of bronchiectasis, although some discoveries have led us to believe that the relationship may be causal. The greatest prevalence of bronchiectasis has been observed in uncontrolled severe asthma. This could indicate that higher bronchial inflammation could be the substrate necessary for the genesis of bronchiectasis. In the majority of asthmatics, eosinophilic inflammation can be observed, these cells having demonstrated elastolytic capacity and the secretion of substances that can damage the bronchial wall such as eosinophil cationic protein and some metalloproteases (13,14). Furthermore, neutrophilic inflammation is frequent in both asthma and bronchiectasis (15,16)

Nonetheless, both diseases can be caused by common etiopathogenic mechanisms, such as neutrophilic and eosinophilic inflammation, altered airway microbiota, mucus hypersecretion, allergen sensitization, immune dysfunction, altered microRNA, dysfunctional neutrophilic activity and variants of the HLA system (15,17–21).

In addition, regulatory mechanisms of gene expression may support the association between asthma and bronchiectasis. Indeed, higher miR-320c levels have been observed both in patients with asthma and in those with bronchiectasis (17).

Both inhaled and systemic corticosteroids are frequently used in asthma, particularly for severe cases (1,22), and often without being monitored by specialists (23). This medication, with its strong immunosuppressive properties, could lead to an increase in chronic bronchial infection, implying that it could encourage bronchiectasis to develop (24).

4. Prevalence of bronchiectasis in asthma

The prevalence of bronchiectasis in asthma is highly variable, oscillating between 0.8% and 77% (9,25–27), with the average sitting at 35.2% according to data from a recent meta-analysis (28). Some groups of asthmatics have been identified in which a particularly high prevalence of bronchiectasis has been observed, such as those with the severest cases of asthma, with chronic rhinosinusitis, with corticosteroid-dependent asthma and with adult-onset eosinophilic asthma (29–32).

Asthma prevalence in patients with bronchiectasis is significant, although there are notable differences among studies, oscillating between 15% and 30.2% (33–36).

It is important to identify the etiology of bronchiectasis, as between 13 and 18.3% of patients have noted changes in their condition and in the approach to the disease (37,38). However, in the studies that have investigated the etiology of bronchiectasis, between 40 and 44.8% of the cases were idiopathic, while asthma was considered the etiology of bronchiectasis for between 1.4 and 7% of cases (25,37–40). In a study performed in Finland, Mantyla et al. identified asthma as the cause of bronchiectasis in 26% of patients (18).

Some comorbidities can have an influence on the incidence and evolution of both asthma and bronchiectasis. The interaction between the upper and lower airways has been well documented for many years and recently a hypothesis has been formulated whereby post-nasal drops could be one of the causes of bronchiectasis (20,21,41). Other frequent comorbidities with both asthma and bronchiectasis are gastroesophageal reflux disease (GERD) and psychiatric illnesses such as anxiety and depression (25,42,43).

The variations in prevalence among studies may be design differences. Some authors include smokers whereas others do not, sometimes illnesses that may cause bronchiectasis such as allergic bronchopulmonary aspergillosis (ABPA) or cystic fibrosis (CF) are excluded, but other authors include them. In addition, when the diagnosis is made, high-resolution computed tomography is not always available (8,9,27,44).

5. Impact of bronchiectasis on asthma clinical outcomes

Characteristic symptoms of asthma are wheezing, shortness of breath, chest tightness, and coughing, very similar to those corresponding with bronchiectasis, which could cause mistakes with diagnoses and delays in being prescribed the correct treatment (1,7).

The latest evidence seems to support the idea that bronchiectasis has a significant impact on the clinical presentation of asthma, although discrepancies have been observed among the publications available, mainly due to methodological differences. Several authors have suggested that the diagnosis of bronchiectasis should be considered in asthma patients of advanced age, who suffer from frequent exacerbations, who show an inadequate response to their usual treatment, with a decline in lung function or infections from pseudomonas aeruginosa (25).

Two recent meta-analyses have shown that asthmatics with bronchiectasis are elderly, have more exacerbations and more airflow obstruction, and do not display any differences in terms of sex, IgE levels, or tobacco use (28,45). These meta-analyses have discrepant results when it comes to BEC levels, higher in patients with bronchiectasis in the study by Zhang while no differences have been found in Lan; FEV1 values, however, are lower for the cases of asthma and bronchiectasis according to Lan's study whereas no significant differences have been noted in Zhang et al. (28,45).

Later studies, which have not been included in these meta-analyses, have shown results contradictory to them. Ferri et al., in a study with an Italian population, observed that asthmatics with bronchiectasis are younger than those without it (33). On the same note, in two recent articles, it has been reported that higher IgE levels were obtained in patients with bronchiectasis and asthma than in patients with just the latter (19,30).

Asthmatics with bronchiectasis have asthma for longer, with more severity, a greater prevalence of chronic expectoration, and more comorbidities like GERD, intolerance toward non-steroidal anti-inflammatory drugs (NSAIDs), chronic rhinosinusitis and nasal polyps (19,26,27,29,30,33,41,46).

Given the clinical and functional similarities between both diseases, it clearly seems necessary to evaluate the usefulness of new markers which allow accurate diagnoses to be made. Recently, the usefulness of FeNO for diagnosing asthma appears to have been consolidated, indicating that it could also be helpful for recording the differential diagnosis of this illness in patients with bronchiectasis with a cutoff point of 22.5 ppb, although the current guidelines recommend that it should be set at 40 ppb to this end (47–49).

The coexistence of asthma and bronchiectasis also poses difficulties for the therapeutic focus, since inhaled corticosteroids (ICS) are key drugs for asthma treatment, whereas there could be a greater risk of

infection in patients treated chronically with them (24,50). However, in patients with both asthma and bronchiectasis, the current evidence appears to support the use of ICS, as it does not significantly increase the risk of infection (51). For patients with asthma and bronchiectasis, the benefit of ICS on asthma is likely to outweigh the increased risk of respiratory infection associated with this treatment in patients without asthma.

Another point of discussion is the use of monoclonal antibodies (mABs) for treating these patients, who have been responding favorably to them, but due to their high financial cost, there is a need to correctly identify those patients who can benefit from using them (52–54).

6. Impact of bronchiectasis on asthma prognosis

The literature is scarce with respect to the impact of bronchiectasis on the vital prognosis of asthma. Nevertheless, a recent Korean study has concluded that the presence of bronchiectasis could be related to an increase in asthma mortality. For this reason, Choi et al. monitored two patient cohorts for ten years with corticosteroid-dependent asthma, including 3,016 asthmatics without bronchiectasis and 754 with it, observing that the latter were 1.65 times more likely to die (IC95%: 1.42–1.92) than the former (46). However, it is important to highlight the limitations of the study, given that it only dealt with severe corticosteroid-dependent asthmatics, while at the same time, the data were extracted from a medical insurance database, which undoubtedly implies a lack of important confounding variables, such as smoking history, pulmonary function test, microbiologic results and so on (46).

In another prospective study, it has been observed that asthmatics with bronchiectasis had more infections, more exacerbations, and worse lung function, most significantly affecting patients with the severest forms of bronchiectasis (32).

It has also been seen that asthma worsens the prognosis of bronchiectasis patients, who have a significant increase in mortality compared to those with bronchiectasis that are not asthmatic (55).

7. Impact of bronchiectasis on asthma treatment

The influence of bronchiectasis presence on asthma treatment can be assessed based on a range of aspects. Firstly, many studies have demonstrated that patients with asthma and bronchiectasis, as opposed to those without either, use more antibiotic courses, systemic steroids, biological treatment, and bronchodilators as a consequence of more frequent and more severe clinical pictures. Secondly, the coexistence of both diseases should require the bronchiectasis of these asthmatics to be treated in accordance with the recommendations of the international guides with specific treatment for them such as inhaled antibiotics in the case of bronchial infection or macrolides for multiple exacerbations (26). It seems to be demonstrated that the presence of bronchiectasis does not interfere with the positive response of the biological treatment for asthma when it has been prescribed to the right patients (56,57).

Finally, the controversial topic of inhaled corticosteroids should be mentioned, because although they are the cornerstone for asthma treatment, due to their immunosuppressive properties, they are not recommended for patients with bronchiectasis. In this case, the guidelines are clear and advise that they should continue to be prescribed to asthmatic patients while trying to reduce the dose to the absolute minimum (58).

8. Asthma-bronchiectasis endotype

In spite of the neutrophilic inflammation for asthma being a risk factor for bronchiectasis to occur, most severe asthmatics with that disease show eosinophilic inflammation, which gives it a particular endotype. Some authors have observed that the eosinophil actively forms part of the inflammation in bronchiectasis. In a *post hoc* analysis of two clinical trials, it has been observed that 42% of these patients had peripheral eosinophilia ≥3% and 23.6% ≥4% even without asthma (59) while a rise in the number of peripheral eosinophils was associated with a greater number of exacerbations (60). However, patients with bronchiectasis are also the only ones who have appeared to respond positively to inhaled steroid therapy with a drop in the number of exacerbations and an improvement in quality of life (58). Therefore, as has already been mentioned, the eosinophil is an active actor capable of producing bronchial damage, which can worsen in a patient with asthma and bronchiectasis.

8.1. Does an asthma-bronchiectasis phenotype really exist (ABOS)?

Considering the high prevalence of the coexistence of asthma and bronchiectasis, the existence of

pathophysiological mechanisms where each of these diseases is associated with a higher incidence of the other and a relevant impact on their prognosis, it seems clear enough to suggest that an asthma-bronchiectasis (ABOS) phenotype really exists. The correct identification of this ABOS phenotype could allow for a better diagnostic approach and a more adequate treatment that should improve the prognosis of these patients. It seems necessary to set out future research pathways to improve the definition of this phenotype by establishing clear criteria based on evidence.

While waiting for this evidence to arrive, we could consider ABOS to be a suitable future candidate as a differentiated phenotype for certain patients.

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ORCID

Francisco-Javier Gonzalez-Barcala http://orcid.org/0000-0001-5847-4784

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