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Asthma–COPD–Bronchiectasis combination: an unstudied triplet

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Editorial

Even if the coexistence of asthma and chronic obstructive pulmonary disease (COPD), known as asthma–COPD overlap (ACO), is progressively more approached for studies in recent years, if one should try to find out what does the existence of bronchiectasis in the above-mentioned ACO patients involve, he or she would be deeply disappointed by the low number of articles addressing this subject. The so-called ACO is a common overlap whose prevalence and prognosis are highly dependent on various factors such as the moment of diagnosis, the therapeutic intervention, or the severity of the obstruction (1). This is heavily influenced also by the lack of evidence about the pathophysiology of ACO and the mixture of the inflammatory patterns (T Helper cells type 1 (TH1), characteristic for COPD and T Helper cells type 2 (TH2), specific for asthma). As a stand-alone entity, bronchiectasis has also many unknown aspects, like the variation of prevalence, estimated as ranging somewhere between 42 and 566 cases per 100,000 (2) and the interferences with other diseases where this condition leads to changes to both prognosis and therapeutic management.

A 28.4% prevalence of bronchiectasis reported in uncontrolled moderate-to-severe asthma (2), means that one in three asthma patients experiences this type of association. Previous studies revealed that the association is related to the severity of asthma, the presence of chronic expectoration, lower levels of fractional exhaled nitric oxide (Fe NO), and a previous history of pneumonia (3). In the literature, the prevalence of bronchiectasis among patients with asthma ranges from 2.2% (4) to 77% (5). This broad variation is caused by some influence factors such as smoking status (more obvious in association with COPD), High-Resolution Computed Tomography (HRCT) techniques used, and allergic bronchopulmonary aspergillosis (ABPA).

On the other way, bronchiectasis were identified in 57.2% of patients with moderate-to-severe COPD (6). This association is recognized as Bronchiectasis-COPD overlap syndrome (BCOS), and is known to be associated with an increased risk of all-cause mortality (6). Other researchers reported a lower prevalence rates of BCOS: 5% in Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage III and 7% in GOLD stage IV of the disease (ECLIPSE cohort) (7) or higher—20.8% (in COPDGene Study) (8). Many authors analyzed the relationship between COPD and bronchiectasis because this associations could have important clinical implications, since both diseases have different and complementary therapeutic approaches. Identification of bronchiectasis in patients with COPD is directly proportional with the severity of the disease (9). ACO guidelines are focusing especially on definitions, differential diagnosis, treatment algorithms, phenotyping, etc., but there are only a few articles where the authors are assessing the impact of frequently associated comorbidities. One of them, bronchiectasis, remains a challenge for all the lung physicians dedicated to this subject. Browsing through GOLD guidelines (which incorporated a consensus document developed jointly with the Global Initiative for Asthma (10), which defines ACO and proposes a different approach) or the Spanish Guidelines for COPD (11), and Spanish Guidelines for Asthma (GEMA) (12), we found only few mentions about the presence of bronchiectasis.

ACO and BCOS are associated with an increase in clinical severity and mortality. The common scenario for identifying bronchiectasis in this triplet is at least controversial. First of all, the practitioners are discovering the COPD/asthma disease (of course with the difficulty of defining exactly what is dominating, what was a primary condition, etc.). Second, the occurrence during therapeutic management of events, such as failure to respond to standard treatment, frequent exacerbations, large volume of sputum production, isolation of Gram-negative organisms in sputum, or severity of COPD or asthma that seems out of proportion to the reported smoking history, are key triggers for inducing further investigation (13). This also leads to a certain delay of the final complete diagnosis. There are some features pleading for the diagnosis of ACO in favor of asthma: a lower

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diffusion capacity, a higher number of comorbidities, and higher levels of neutrophils and interleukin-6 (IL-6) in the blood (14). The presence of bronchiectasis is difficult to identify because the level of neutrophils is higher and they present also in some cases lower diffusing capacity. The things are more complicated if we are thinking that overlap syndrome is more prevalent in older patients (15) with a higher chance to have bronchiectasis.

Scientific publications mention that, statistically, ACO-bronchiectasis phenotype is less frequent than COPD–bronchiectasis or asthma-BCOS (16). In a study based on the evaluation of comorbidities among chronic obstructive pulmonary phenotypes, the author showed an ACO prevalence of 13%, with an average age of 62.8 ± 15.8, and, interestingly, half of these patients also suffering from diabetes (17).

How does the prevalence of comorbidities in the triplet look like? There are no studies in this area, probably due to several causes:

1. Often there is a misdiagnosis of COPD and asthma because of the overlapping symptoms, and patients with bronchiectasis are particularly at risk of evading evidence (18).
2. Patients with clinical features of both asthma and COPD have been excluded from big-data clinical trials; the result was a small patients' population that is not representative in routine clinical practice. Even so, where asthma and COPD occur together it seems that there are increased rates of bronchiectasis compared with asthma or COPD alone (19).

The exacerbation rate also seems to be higher in this triple association, with very few evidence for this subject. Sadigov et al. found that ACO and non-cystic fibrosis bronchiectasis lead to more exacerbations compared with bronchiectasis alone (4.2 ± 1.8 vs 2.0 ± 0.9; $P < 0.001$) (19); also the FEV1 at the time of admission to hospital was lower in the first cohort (42 ± 16.8% vs 67 ± 14.6%; $P < 0.001$). They found a more complex microbiome, especially a higher presence of *Pseudomonas aeruginosa*, more severe clinical features, a higher mortality rate and need for non-invasive ventilation and oxygen support, intensive care unit (ICU) admissions and multilobe involvement on computed tomography (CT) lung scan in the first group of patients (19).

Referring to ACO-bronchiectasis treatment, the majority of the studies are avoiding to clarify how these cases should be managed. There are some reports signaling higher reduction of exacerbations in a cohort of patients with ACO treated with combination therapy inhaled corticosteroids (ICS) – long-acting beta-agonists (–0.42 vs +0.17) and in a cohort of patients with BCOS treated by mucolytic drugs (–0.57 vs +0.88) (20). Regarding ICS, there still is a big dilemma regarding their use for the triplet.

The report of Brode et al. (21) underlines the statistically significant association between non-tuberculous mycobacterial pulmonary disease (NTM-PD) and current use of ICS for patients with COPD only (asthma absent, adjusted odds ratio [aOR]: 1.96, 95% confidence interval [CI]: 1.62–2.36) and for patients with ACO (aOR: 1.74, 95% CI: 1.32–2.28), but insignificant for patients with asthma only (COPD absent, aOR: 1.56, 95% CI: 0.93–2.62). However, an interaction analysis did not detect a statistically significant difference in risk between individuals with asthma, COPD or ACO ($P = 0.21$) (21).

Regarding the impairment of physical activity (PA), a common problem in obstructive airway diseases, it should be addressed by multifactorial actions, in correlation to the level of impairment and the associated characteristics. Compared to controls, patients diagnosed with severe asthma, bronchiectasis, and COPD accumulated less steps/day, a median difference of −2255, −2289, and −4782, respectively ($P \leq 0.001$) (22).

The new concept promoting individualized therapy for COPD and ACO, targeting only specific features and proving improved health outcomes, should probably be applied also to this association of three conditions (23).The "treatable traits" approach might be the only useful strategy to help clinicians consider the many different aspects that must be addressed for appropriate clinical management of patients with bronchiectasis, considering also ACO.

Conclusions

We could conclude that ACO represents a distinctive clinical phenotype characterized by more frequent exacerbations, longer hospitalization durations, worse health-related quality of life, higher risk of death (24), and higher healthcare costs than either disease alone. If the association of bronchiectasis (another disease) could change the clinical outcome for these patients remains to be clarified.

Regarding this triplet, several issues would probably need to be addressed in the future:

1. There is a need for a consensus for ACO stand-alone and in association with bronchiectasis;
2. Design of clinical trials intending to elucidate the epidemiology and pathophysiology and to ascertain the optimal management strategies for this triple combination;
3. Implementation of the "treatable traits" (25) approach to patients with bronchiectasis, hoping to contribute to a more personalized and precise management of these patients and, eventually, to improved clinical outcomes;
4. Physicians facing this type of patients may have difficulties to consider which is the "predominant disorder"(26);

5. A future direction for research could be to better understand the relationship between bronchiectasis, as stand-alone disorder, to the overlaps with COPD and asthma (27).

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