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SPECIAL ARTICLE

Blurred lines. Eosinophilic COPD: ACOS or COPD phenotype?

C.C. Loureiro[a,b]

[a] *Pneumology Unit, Hospitais da Universidade de Coimbra, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal*
[b] *Centre of Pneumology, Faculty of Medicine, University of Coimbra, Portugal*

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Abstract Because asthma and COPD are both inflammatory chronic obstructive airway diseases, there are several clinical expressions which can cause confusion, such as: eosinophilic asthma with fixed obstruction, which is a risk factor and might progress to COPD; eosinophilic COPD; COPD with partial reversible obstruction with no asthmatic component and also eosinophilic asthma–COPD overlap syndrome (ACOS).

While at the two extremes of these disorders the pathoimmunological processes are clearly different, in some patients there is overlap and the pathophysiological border between asthma and COPD is fused (or diffuse).

The current guidelines are clearly insufficient for classification of the obstructive patients and, taking into account that binary separation between the two diseases is not completely clear, we should resist the temptation to label patients as ACOS and consider new airway disease taxonomy. Regardless of the condition concerned, eosinophils should be considered in the algorithm approach to obstructive patients: in COPD, as in asthma, they are related to the underlying pathological process; they have prognostic value and are related to therapeutic response. Therefore, eosinophils should be valued as useful biomarkers and included in a multidimensional diagnostic and therapeutic approach, bearing in mind the phenotypic, immunopathological and functional complexity of chronic obstructive airway disease.

Abbreviations: ACOS, asthma–COPD overlap syndrome; BD, bronchodilator; COPD, chronic obstructive pulmonary disease; ECLIPSE, Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points; FeNO, fraction of exhaled nitric oxide; FEV_1, forced expiratory volume in the first second; FP, fluticasone propionate; HRB, bronchial hyperreactivity; ICS, inhaled corticosteroids; RV, residual volume.

E-mail address: cl_loureiro@hotmail.com

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Asthma–Chronic obstructive pulmonary disease (COPD) Overlap Syndrome (ACOS) has been regularly used to cover several clinical events that are hard to read and incorporate. Whereas Asthma and COPD are both chronic inflammatory and obstructive diseases of the airways, the obstructive disease can manifest itself in so many ways that it can be confusing, both within the clinical spectrum of asthmatics and in COPD patients.

On the one hand, among the independent risk factors for COPD, personal asthma history comes up as relevant, as found in the CANCOLD[1] study (which followed the protocol of the BOLD study[2]). On the other hand, the clinical phenotype of asthma with fixed airflow obstruction is well understood in clinical practice, characterised by a long progression time of the disease, frequently lower bronchial hyperreactivity (HRB), greater disease severity and usually with raised Th2-type inflammation markers (such as Fraction of exhaled nitric oxide (FeNO), sputum[3] and peripheral blood eosinophilia[4]), of predictive value for that phenotype.

Furthermore, peripheral blood eosinophilia is also present in a significant number of COPD patients: in the cohort of the ECLIPSE study (Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points[5]), which included approximately 1500 patients with COPD and excluded asthmatics, the prevalence of persistent eosinophilia (defined as eosinophils in blood $\geq$2% or 150 cells/microlitre) was 37%. This patient group includes fewer smokers, mostly male individuals, who enjoy improved quality of life, are less symptomatic and less functionally impaired (based on forced expiratory volume in the first second (FEV_1) assessment) and evolve less to emphysema during follow-up.

Finally, according to the CHAIN study[6] (multi-centre database of well-characterised COPD patients), with one-year follow-up, which did not exclude asthmatics and followed current criteria for defining ACOS), eosinophilia exists irrespective of asthma overlap. In this study, 27% of patients who suffered from COPD but did not have ACOS, had peripheral blood eosinophils above 3%. Interestingly, comparing COPD patients with and without ACOS, parameters like age, chronic bronchitis symptoms, emphysema and FEV_1 did not differ significantly.

Consequently, we can state that asthma is an independent risk factor for COPD and that there is a phenotype of asthma with persistent obstruction, which is more severe and has eosinophilia as risk factor that can also be present in COPD, irrespective of the presence of asthma.

Therefore, while at the two extremes of these disorders the pathoimmunological processes are clearly different, in some patients there is overlap and the pathophysiological border between asthma and COPD is fused (or diffuse).

This brings us back to the clash between British *vs.* Dutch hypotheses, which support the different or common origin of the diseases, respectively.

For a better understanding of these relationships one must identify the genes involved, their epigenetic interaction and the underlying pathoimmunological mechanisms of the phenotypes of the two forms of the disease.

While genome-wide association studies (GWAS) had not identified clear associations between Asthma and COPD,[7] recent evidence underscores the shared genetics. A cohort study of individuals from the UK Biobank[8] (the largest European Biobank), which grouped the sample elements according to extreme FEV_1 values and smoker and non-smoker status, found that: (i) there are common genetic causes for airway obstruction in smoker and non-smoker patients (and that genetics and smoking habits generally act independently); (ii) the genetic determinants of low FEV_1 in non-asthmatic individuals are also involved in asthmatics; (iii) there is a fragment of the gene which is involved in airway function and obstruction in the general population (17q21.31).

As for the pathoimmunological mechanisms, a very elegant study published recently by the Leicester group[9] supported both the British hypothesis of a different origin of the two diseases, and the Dutch hypothesis that points to a common origin. This study, which *aimed* to investigate the overlapping pathophysiological characteristics between asthma and COPD, conducted a cluster analysis of clinical, physiological and cytokines data of induced sputum in severe asthmatic patients and individuals with moderate to severe COPD. Three distinct groups were identified: one with predominantly eosinophilic asthma and Th2 cytokine expression (but included 5% of patients with eosinophilic COPD); another of predominantly COPD with mixed inflammation and increased IL-6 levels in the sputum (suggesting the different origin of the two diseases); and a third, composed of asthmatic and COPD patients, with cytokine IL-1β that differentiated it from the other two (thus supporting the common origin).

Finally, another recent study found the Th2 profile genetic signature associated with ACOS patients, supporting the hypothesis of a common origin, at least in one patient phenotype.[10] In this complex investigation, based on the results of the genetic expression study of asthmatic patients, a Th2 gene expression was found to be related to increased expression of Interleukin (IL) 5 and 13 in bronchial biopsies, higher number of eosinophilis, increased bronchial hyperreactivity (HRB) and greater response to inhaled corticosteroids (ICS). In the same study, individuals with the same Th2 gene expression were found in the subsequent analysis of two COPD patient cohorts of that study. In a third cohort of COPD patients (which excluded asthmatic patients), the aforementioned genetic expression was associated with greater disease severity, higher number of eosinophils and increased response to ICS, assessed on the basis of residual volume (RV) after 30 months of therapy. It is thus appropriate to state that these individuals with COPD and signs of asthma, whose clinical history did not suggest asthma, can be the real ACOS. The fact that no relation with FEV_1 improvement after treatment was found, but that RV did decrease, suggests that Th2 gene expression influences COPD patients. In future studies, other outcomes (like RV) should be used besides FEV_1.

Regardless of the condition concerned, eosinophils are useful biomarkers in chronic obstructive inflammatory airways disease.[11] Produced in the bone marrow by IL3 and IL5 (the latter being responsible for prolonging their survival), they migrate to the airways and infiltrate the tissue under the action of chemokines and integrins, where they release cationic granule proteins and cause cell damage, increasing oxidative stress, while exposing the epithelial membrane, becoming more vulnerable.

While in asthma the eosinophil count is well established, now is the time to assess its added value in patients diagnosed with COPD (with or without asthma). The value of a biomarker depends on the relationship with the pathological process, the prognostic value and the link to certain therapies. The aforementioned studies identified the tie between eosinophils and a pathoimmunological process.[10] As for the prognostic value, the relationship with the respiratory function and exacerbations, two factors determining the classification of these patients, must be identified.

Although we have seen that the RV may be influenced by the Th2[10] gene expression, FEV_1 has been the most extensively studied functional parameter in assessing COPD patients. Several studies have denied the relationship between eosinophil count and decreased respiratory function, but a recent CHEST[12] editorial highlighted that persistent eosinophilia, although unrelated in COPD with reduced lung function (as shown in the ECLIPSE study), may be deleterious in the appropriate environment. In a cohort of patients with non-asthmatic eosinophilic bronchitis[13] (that included 141 patients followed over 10 years), 60% of these patients relapsed after 4 weeks of ICS therapy, the relapse rate being significantly higher among individuals with persistent airway eosinophilia. Although the disease did not evolve to obstruction, there was more significant dysfunction of the small airways in the group with disease recurrence.

As for exacerbations, a recently published study[14] with over 80,000 participants and 7225 patients identified with COPD (excluding patients diagnosed with asthma), linked a total count of eosinophils above 340 cells/μL with a twofold increase of exacerbations during the follow-up period of 3.3 years.

Therefore, the eosinophil count has definitely a prognostic value in COPD, as it does in the case of asthma.

In relation to the link with therapy, (we know it does exist in asthmatics), in patients with COPD such evidence is becoming definitive. In a metanalysis published in 2014,[15] which aimed at comparing the outcomes of COPD patients with exacerbations under prednisolone or the equivalent *vs*. patients under therapy excluding systemic corticosteroid treatment, it was found that, when patients were grouped according to the count of eosinophils in the peripheral blood (cut-off $\geq$2%), in patients with $\geq$2%, treatment failure rate was much higher in those not treated with systemic corticosteroids during exacerbation (66% *vs*. 11%).

Other *post hoc* analyses of clinical trials showed that the phenotype-oriented therapy can be relevant.

A *post hoc* analysis of INSPIRE study[16] (conducted on patients with exacerbations, with moderate to severe COPD), which compared two branches of treatment – fluticasone propionate (FP) + salmeterol against tiotropium bromide – in the group with eosinophil count in the peripheral blood $\geq$2%, showed that exacerbation rate reduction was more significant in patients with combined treatment with ICS and bronchodilator (BD).[17]

In the *post hoc* analysis of ISOLDE[18] study (that assessed the efficacy of FP therapy, which included patients at all levels of COPD severity, excluding asthmatics), FEV_1 decrease in patients with $\geq$2% eosinophil in the peripheral blood was significantly lower in those patients receiving FP.[19]

The *post hoc* analysis of FORWARD study[20] (conducted on patients with severe COPD and a history of exacerbation), which compared the efficacy of treatment with beclometasone/formoterol against formoterol, showed that when patients were organised in quartiles of eosinophil count in the peripheral blood, the exacerbations rate dropped significantly (46%) in the arm treated with the combined therapy of the upper quartile group of patients (over 280 cells/μL).

Finally, in a more recent study published in Lancet Respiratory Medicine,[21] eosinophil blood count proved to be an important marker for identifying candidates for therapy approaches seeking to reduce exacerbations. This *post hoc* analysis included more than 3000 patients meeting ATS/ERS criteria for COPD, excluding those who were currently diagnosed for asthma (but not the ones with a previous diagnose). In approximately 2/3 of patients the count of eosinophils in the peripheral blood was equal or higher than 2% and exacerbations decreased significantly in this patient group when treatment included ICS (0.91 *vs* 1.28 exacerbations/patient/year; $p < 0.0001$).

Although none of these studies provide a mechanistic explanation for the added value of ICS in eosinophilic COPD, future results of trials with biological treatments (like anti-IL5) will deliver further insight. Regarding benralizumab, an assessment study of the efficacy of anti-IL5 in patients with moderate to severe COPD, although not having found significant difference in the primary endpoint (acute exacerbation of COPD) in the different eosinophilic groups, found a clinically significant improvement after anti-IL5 in patients with eosinophil count $\geq$200 cells/μL.[22]

Therefore, as suggested by Bateman et al.[23] in a paper that reviews the factors shared by the clinical expressions of the obstructive pathology (asthma, COPD or ACOS), the taxonomy of obstructive diseases must be reassessed. Until that happens, we suggest the use of biomarkers like eosinophils, as the eosinophilic phenotype is cross-cutting, with a clearly more favourable response with ICS treatment.

Ethical responsibilities

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Conflicts of interest

The author has no conflicts of interest to declare.

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