Subphenotypes: the many faces of chronic obstructive pulmonary disease

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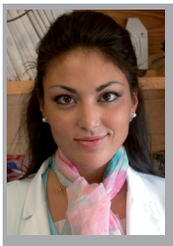

Francesca Polverino
Department of Respiratory Diseases, Hospital Universitario Son Dureta, 07014 Palma de Mallorca, Spain

Borja G Cosío†
†Author for correspondence: Department of Respiratory Diseases, Hospital Universitario Son Dureta, 07014 Palma de Mallorca, Spain
Tel.: +34 971 175 433
Fax: +34 971 175 228
borja.cosio@ssib.es

What do we mean by phenotypes or subphenotypes? This term has been extensively introduced into the scientific literature to describe different forms of clinical presentation of chronic obstructive pulmonary disease (COPD), but it has certainly been wrongly used, because we still do not know whether these different 'phenotypes' share the same genotype. Nevertheless, it should bring our attention to the different manifestations of a single disease. Or does it really mean that we do not understand several diseases, and we are considering them under the same umbrella?

Classically, the blue-bloaters and the pink-puffers were considered the two most common phenotypes of COPD, but with the premise that they could overlap each other. In fact, since the time of the Ciba symposium in 1959 [1], COPD has been thought of as an overlap between three main phenotypes: chronic bronchitis, emphysema and asthma associated with chronic airflow limitation. This was first represented in a nonproportional Venn diagram by Snider [2]. Current international guidelines [3] propose that the diagnosis of COPD requires the presence of incompletely reversible airflow obstruction to be confirmed by spirometry, with a ratio of post-bronchodilator forced expiratory volume in the first one second to the forced vital capacity of the lungs (FEV1:FVC) of less than 0.7 and exposure to noxious particles or gases – namely, cigarette smoke. However, this concept does not recognize the range of clinical presentation and pathophysiological abnormalities that may be present in this heterogeneous condition, and, moreover, it is independent of the presence of chronic cough and sputum or the existence of emphysematous structural changes in the lungs. The final result is a 'syndromic' disease, in which COPD can be viewed as a 'basket' that encompasses a range of pulmonary and systemic manifestations, and which is characterized by a narrow pattern of symptoms, exposure to certain risk factors, variable patterns of airflow obstruction and airway hyperresponsiveness, and different types of airway inflammation with structural changes [4,5].

Recognizing the different phenotypes within COPD is important for understanding the underlying disease processes, and to determine whether the phenotypes vary in their response to different pharmacological treatments; this knowledge could lead to treatment specifically targeted for defined phenotypic groups, rather than a 'syndromic disease' or asthma/COPD in general. An obvious limitation is the lack of a gold standard against which to assess phenotypic definitions of COPD.

Another limitation when we want to look at the many faces of COPD is that the findings are influenced by the criteria used to define COPD, as well as the population in which the study was carried out. Studies are often limited by the lack of complete lung function tests with post-bronchodilator spirometry to diagnose COPD, the absence of radiological investigations such as chest computed tomography (CT) scans to diagnose emphysema, and an over-reliance on nonstandardized physician diagnoses. In fact, estimates of COPD prevalence vary widely [6], and much of this variation likely reflects differences in the populations studied, spirometry methods, data quality control and the rules used to define COPD. This approach will inevitably result in different proportions of the COPD phenotypes.

Information regarding smoking habit, hyperinflation, anemia, cachexia, exercise capacity, dyspnea and measurement of health-related quality of life, some of which are scored in the multidimensional BODE index [7], allows

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us to obtain a better picture of how patients are affected by their illness and provides complementary information to the phenotype.

Current concepts suggest that COPD results from the complex interactions of many genetic factors (most of which remain undefined) that interact with many environmental factors (the most important of which is cigarette smoking). Cigarette smoking is without doubt the primary etiologic factor for COPD, and has been attributed as one of the main causes of increased systemic inflammation observed in these patients [8], possibly explaining any link between COPD and other chronic conditions such as the metabolic syndrome.

A more accurate phenotypic description of COPD may be achieved by using biomarkers that allow distinct subgroups of patients with different prognosis or response to therapy to be defined, but in order to use these biomarkers to enhance phenotype description, it would be important to know if clinical characteristics, such as systemic inflammation, are associated with these biomarkers.

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Roy *et al.* [9], using the technique of components analysis (a factor analysis to reduce a large number of variables to a much smaller number of components), have identified four components that explain two-thirds of the variance between patients. The first two components represented neutrophilic–systemic inflammation (sputum neutrophils, neutrophil chemoattractant IL8 and plasma TNF-α), suggesting that the profile of neutrophilic airway inflammation is associated with systemic inflammation and eosinophilic inflammation (sputum eosinophils and FeNO), which is associated with increased corticosteroid responsiveness [10]. Lung function parameters (bronchodilator reversibility, FEV1 and inspiratory capacity) and C-reactive protein, a known marker of cardiovascular disease risk [11] and indicative of mortality in COPD [12], formed separate components. Markers of systemic inflammation have consistently been found to be elevated in patients with stable COPD [13–15]. Several potentially relevant mechanisms such as smoking, hypoxia, genetics, local inflammation spilling over to the systemic compartment and exacerbations are currently believed to play a role in the presence of systemic inflammation in patients with COPD [16].

Inflammation likely plays a key role in the development of COPD. However, in COPD patients there are several different inflammatory responses that vary qualitatively and quantitatively; it is likely that there are many pathways for their pathogenesis [17]. Exacerbations of the disease may also play a role in the inflammatory profile shown by some, but not all, patients. The reason why some patients behave as frequent exacerbators and some others show a nonexacerbator 'phenotype' remains an open question.

All these components may represent the pathophysiological processes responsible for the disease heterogeneity within the dataset, emphasizing COPD as a truly multidimensional disease.

The heterogeneous nature of COPD is highlighted by the variability of anatomic phenotypes, symptomatology and systemic manifestations. Research efforts aim to further refine disease phenotypes (especially by characterization of those individuals falling outside the known limits) in order to better understand the molecular mechanisms behind this disease and for tailored therapy. It seems plausible that some therapies will be effective for a subset of COPD patients, but useless (or worse) for others, and Rennard and Vestbo [18] provocatively suggest that the classification of COPD, or at least the determination of definable phenotypic subsets of COPD patients who share common mechanistic pathways, is appropriate for a specific intervention as an 'orphan disease'.

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