Infectious Causes of Chronic Obstructive Pulmonary Disease: ‘TB or not TB, That Is the Question’

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The concept of chronic obstructive pulmonary disease (COPD) has been evolving over recent decades. Although earlier studies provided descriptions of emphysema and chronic bronchitis [1], the CIBA symposium landmark meeting in 1959 [2] established the foundation for COPD. As defined in the Global Initiative for Obstructive Lung Disease strategy [3], COPD is characterized by a persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and lungs to noxious particles or gases.

According to this definition, there are two sine qua non conditions for establishing a diagnosis. The first is the demonstration of chronic airflow obstruction (CAO). This non-reversible airway obstruction must be demonstrated by pulmonary function tests with the patient in a stable condition and after performing a bronchodilator test [3]. The second condition is that CAO has to result as a consequence of prolonged exposure to inhaled noxious particles or gases, because the enhanced chronic inflammatory response to these inhalants causes the disease and the pathological alterations described [4]. In this context, tobacco smoke is the leading inhaled toxin, and thus, the main risk factor for the development of COPD [5]. COPD and tobacco have been invariably associated in numerous epidemiological studies described in the literature [6].

A problem arises in cases of CAO in patients who have not been active smokers. In these cases, following the definition of COPD, other factors such as passive smoking or exposure to other inhaled irritants play a major role. Indeed, a number of previous studies have established passive smoking or biomass exposure as causes of CAO and therefore COPD [7, 8]. In those cases when the patient has not been exposed to inhaled toxins, a differential diagnosis of CAO should be made, including asthma, bronchiectasis and infectious diseases such as pulmonary tuberculosis (TB). These disorders are also associated with CAO, and there is some debate about whether TB should be considered a risk factor for COPD. The confusion is partly explained because epidemiological studies of the prevalence of COPD have exclusively used the results of spirometry to detect one case, forgetting the other pillar of the diagnosis, namely chronic exposure to inhaled fumes. Moreover, in these studies, CAO equals COPD [9].

In the present issue of *Respiration*, Allwood et al. [10] performed a systematic review of the peer-reviewed literature on the association between pulmonary TB and the development of CAO. After their search, 19 observational studies met the eligibility criteria. In the analysis, all but two of these works reported a positive association be-

tween pulmonary TB and CAO, confirming the findings of previous studies [11]. However, as the authors state, it remains unclear whether TB should be added to the list of risk factors for COPD or whether TB with CAO should be considered to be a different phenotype within the COPD spectrum or an unrelated disorder [7].

On the one hand, TB is not a toxic inhalant but an infection, and the CAO many patients develop occurs due to scarring and bronchiectasis, which implies a different pathophysiology. On the other hand, it has been recently described how tobacco smoking could substantially increase TB cases and deaths [12], increasing TB sequelae and thus CAO. Additionally, TB is a cause of bronchiectasis, which may worsen the clinical presentation of COPD or its prognosis.

Interestingly, the Global Initiative for Obstructive Lung Disease strategy recognizes TB as a cause of COPD and states that TB is both a differential diagnosis to COPD and a potential comorbidity [3]. Further, this could also be extended to other infectious agents. Therefore, to ascertain whether an infectious agent should be considered a cause of COPD, the functional, clinical, prognostic and inflammatory aspects of both diseases should be compared. The implications for disease management are important, since COPD has undergone a huge number of clinical trials on the efficacy and safety of inhaled therapies. However, this has been seldom done for CAO due to TB. Quoting the English poet and playwright, William Shakespeare (1564–1616), in the tragedy of *Hamlet*: ‘TB or not TB, that is the question’.

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