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Co-occurrence of Chronic Obstructive Pulmonary Disease and Bronchiectasis: Is It a New Phenotype of Chronic Obstructive Pulmonary Disease?

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Abstract

Bronchiectasis and chronic obstructive pulmonary disease (COPD) share many pathophysiological, clinical and spirometric characteristics. Along with the increasing and widespread use of high resolution computed tomography (HRCT) scanning, bronchiectasis has become more detectable in patients presenting with chronic cough and shortness of breath. Identification of different phenotypes of COPD is important in terms of both therapeutic options and clinical outcomes of the disease. Co-occurrence of chronic obstructive pulmonary disease and bronchiectasis might be a different phenotype with more severe COPD and poorer prognosis. Many authors observed high prevalence of bronchiectasis in COPD patients showing association with increased inflammation, more severe and longer exacerbations, higher colonization of bronchial mucosa with potential pathogenic bacteria, and, the most important, with poorer prognosis.

Keywords: COPD, bronchiectasis, phenotype

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is an important preventable and treatable public health problem, which is the fourth leading cause of death worldwide (1). It is estimated that COPD-related deaths will increase by more than 30% in the next 10 years (2). In line with this increase, recent studies identified new prognostic indicators in COPD patients such as BODE index (Body mass index, airway obstruction measured by FEV_1, degree of dyspnoea and exercise level), smoking, nutritional status, quality of life, comorbidities, frequency and severity of exacerbations, and C-reactive protein in addition to decrease in pulmonary functions (3-9).

Bronchiectasis is defined as permanent and progressive dilatation of airways caused by the vicious circle of inflammation, infection, mucociliary damage and subsequent bronchial wall injury. Its prevalence is not known and is thought to show regional differences. Its prevalence in the United Sates is reported to be 4.2 out of 100,000 individuals between the ages of 18 and 34 years, and 272 out of 100,000 at and over the age of 75 years (10). Bronchiectasis, which is formerly defined as a rare disease, is being diagnosed more frequently today along with the increasing and widespread use of high resolution computed tomography (HRCT).

Although chronic obstructive pulmonary disease and bronchiectasis are different diseases, they have common and opposing characteristics (Figure 1). Both diseases are seen in advanced ages with the frequent complaint of cough and sputum, and airway obstruction, which is definitive for COPD, is determined in both diseases. Bronchiectasis is usually post-infectious or associated with systemic diseases, usually complicated with gram-negative bacteria or non-tuberculosis mycobacteria, and more prevalent in females than males. Chronic obstructive pulmonary disease is generally associated with smoking, complicated with various gram-negative or gram-positive bacteria, and more prevalent in males than females (11). Although it is not known whether there is a causal relationship between bronchiectasis and COPD, many studies demonstrating the coexistence of these two diseases have been published in the recent years (12-15). The most important question to be answered is whether co-occurrence of COPD and bronchiectasis has an effect on the treatment and prognosis of COPD patients.

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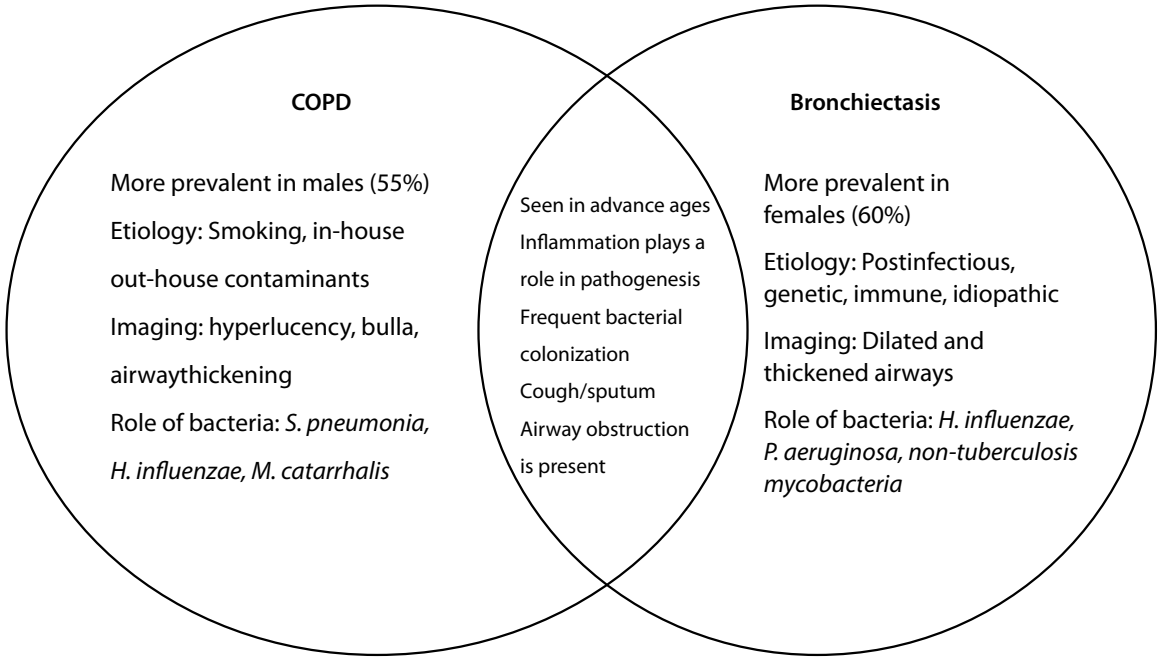

Figure 1. Common and opposing characteristics of COPD and bronchiectasis

PHENOTYPES of COPD

Chronic obstructive pulmonary disease is defined as the irreversible limitation of airflow, and this limitation often guides the treatment. On the other hand, today, it is known that COPD is a complex disease that is quite heterogeneous in terms of clinical presentation, physiology, imaging methods, treatment response, decrease in pulmonary functions, and survival and that FEV_1 alone is not adequate to define, evaluate and manage a disease with such diverse properties. It is obvious that determining key findings that will help classify COPD patients into clinically significant and beneficial subgroups (phenotypes) and subsequent grouping of these patients will make substantial contributions in terms of guidance to the treatment.

It is important to determine the phenotypes of chronic obstructive pulmonary disease as early as possible during the clinical course of the disease so that it could make significant contribution to the clinical outcomes. In the recent years, potential phenotypes associated with clinical outcomes have been determined in numerous titles such as clinical findings, physiological symptoms, radiological characteristics, COPD exacerbations, systemic inflammation and comorbidities (16). BODE index, a simple and multi-dimensional grading system, is one of the methods of clinical phenotyping in COPD patients. It has been demonstrated that BODE index predicts mortality risk of COPD patients (from respiratory or other causes) better than FEV_1 (3).

Exacerbations of chronic obstructive pulmonary disease can be considered either as a consequence of COPD or a phenotype within the context of the definition "frequent exacerbations". Exacerbations have unfavourable effects on the patients' quality of life both in the acute and chronic phases. The most important is that recurrent exacerbations have been suggested to have a negative influence on future pulmonary function testing in the future and might be identified by previous exacerbation history and that, starting from this point, COPD patients with recurrent exacerbations might be a different phenotype (17,18). In the ECLIPSE cohort, it was determined that a group of patients had more frequent exacerbations independent from the severity of COPD defined by spirometry. It has been demonstrated that this subgroup could give significant clinical response to treatment with inhaled bronchodilators used alone or in combination with inhaled steroids (19,20). Again in the COPD subgroup with chronic bronchitis having exacerbation history, significant clinical effects have been achieved with roflumilast, which is a new phosphodiesterase inhibitor (21).

Phenotyping of COPD using High Resolution Computed Tomography

It is thought that morphological changes detected by high resolution computed tomography might make significant contributions to the management of COPD patients. One of the most important examples on the radiological phenotyping of chronic obstructive pulmonary disease has been introduced with the benefit gained from lung volume-reduction surgery by COPD patients, who had upper lobe predominant emphysema and low exercise capacity (22). A relationship has been found between emphysema, bronchial wall thickness and bronchiectasis, which are identified by high resolution computed tomography, and important clinical determinants such as pulmonary function tests, exacerbation frequency, complaint of sputum, response to bronchodilator treatment, and BODE index. Based on these findings, it is thought that phenotypes determined by HRCT would make substantial contributions to the management of patients with COPD (11,16). In a study conducted at our clinic, close relation has been demonstrated between HRCT phenotypes and morphological scores and clinical functional parameters and inflammation markers (Figure 2). In a study assessing HRCTs of 80 stable

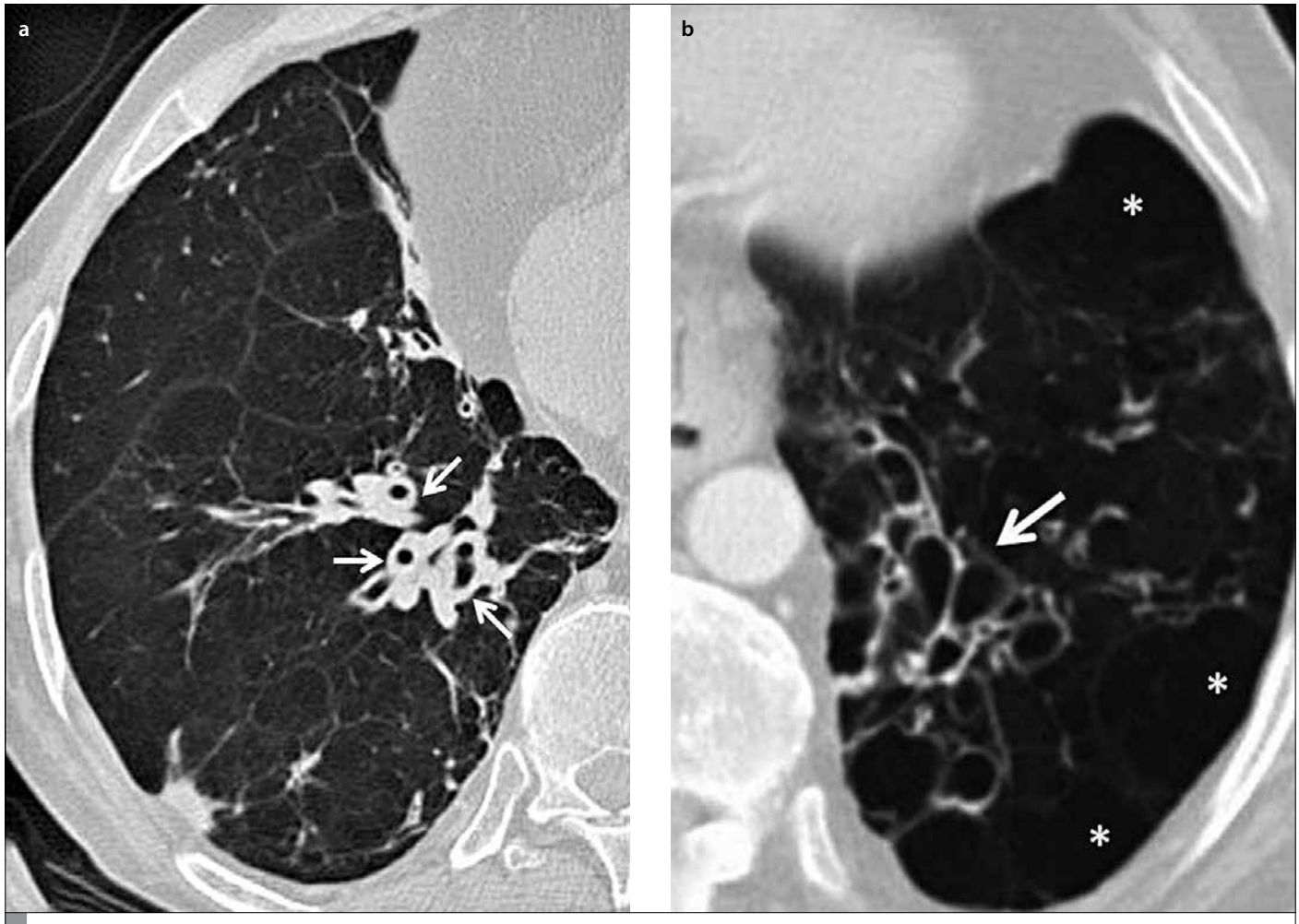

Figure 2. a, b. High Resolution Computed Tomography Scanning: Bronchiectasis in the right inferior lobe together with serious bronchial wall thickening (arrows) (a). Cystic bronchiectasis areas (arrow) and subleural emphysematous areas (*) in the left inferior lobe (b). (Images are obtained from the Archieve of S.U. Faculty of Medicine, Department of Chest Diseases).

COPD patients, emphysema was found in 58.8%, bronchiectasis was found in 33% and peribronchial thickening was found in 31.3% of the patients and signs consistent with poorer clinical course (poorer spirometry results, higher CRP levels, and higher number of exacerbations) were detected in bronchiectasis and peribronchial thickening phenotype (23).

Co-occurrence of COPD and Bronchiectasis

Despite discrepancies between populations demonstrated in the studies, substantially high prevalence of bronchiectasis was demonstrated (28-57.6%) particularly in patients with moderate-severe COPD (12-15). Although a causal relationship has not been demonstrated between these two diseases until today, considering the high rates of colonization, up to 40%, with potential pathogenic microorganisms (PPM) in COPD patients, it has been suggested that COPD poses a risk factor for bronchiectasis (11). It is thought that, the vicious cycle of inflammation-infection-bronchial wall injury, which starts with the potential pathogenic microorganism (PPM) colonization, forms the basis of the pathogenesis of bronchiectasis. This finding is supported by the facts that patients with concurrent COPD and bronchiectasis have enhanced bronchial inflammation, more frequent, severe and longer exacerbations, higher PPM colonization in bronchial mucosa, and poorer pulmonary function tests.

Pseudomonas aeruginosa (P. Aeruginosa) is being associated with acute and chronic pulmonary diseases such as ventilator-associated pneumonia, cystic fibrosis and bronchiectasis and plays a critical role in the course of these diseases. The importance of bacterial colonization and infection in patients with chronic obstructive pulmonary disease has been demonstrated in many studies and their association with more severe COPD has been propounded. *P. aeruginosa* is isolated from 3-20% of COPD patients and it is more frequently isolated in the event of severe disease and during exacerbation periods (11). Although the relation between *P. aeruginosa* and clinical markers and poor clinical course of COPD has been demonstrated in increasing number of studies, this relation has not been explicitly revealed as is in the other diseases. In a study, *P. aeruginosa* was isolated in the sputum of 16.5% of the patients hospitalized for COPD exacerbation. Number of hospitalizations, BODE index and rate of receiving systemic steroid therapy, were found to be significantly higher in these patients (24). In another study, *P. aeruginosa* strains isolated from the sputum of COPD patients were compared with the strains isolated from the blood cultures of patients hospitalized for other reasons and it was determined that isolates obtained from COPD patients showed increased rates of mutation and higher antibiotic resistance, exhibited less motility and formed more biofilms (25). It has been demonstrated that *P. aeruginosa* colonization is

associated with more advanced disease and more severe impairment of function. However, it is not known whether the relation between bronchiectasis and *P. aeruginosa* colonization in COPD patients results from the structural changes due to underlying bronchiectasis or severe disease spectrum involving co-existence of bronchiectasis and COPD. *P. aeruginosa* colonization and infection increases inflammation in COPD patients and this inflammation may lead to bronchiectasis via inflammation-infection cycle.

Although chronic obstructive pulmonary disease has been traditionally defined as chronic airway obstruction, today the dominating opinion is that, there is both airway and systemic inflammation. In a recent review, pathogenesis of COPD has been discussed in three phases as initiation, progression and consolidation (26). Initiation phase includes inflammation that occurs due to the inhalation of toxic and oxidative substances, cigarette being the leading. Progression phase includes various mechanisms consistent with the pathophysiology of bronchiectasis such as degradation of extracellular matrix by elastase observed in patients with alpha-1 antitrypsin deficiency. Detecting high rates of bronchiectasis (95%) both in small case series and in the study conducted by Parr et al. (27) in 74 patients with severe alpha-1 antitrypsin deficiency (PIZ phenotype) appears to corroborate this finding. Thereby, in addition to PPM colonization, individual differences in preservation of the lung structure and repair mechanisms, involved in the pathogenesis of COPD might have a role in bronchiectasis phenotype, as is in other COPD phenotypes.

In COPD patients with concurrent bronchiectasis, a significant relation has been determined between bronchiectasis and severe disease markers of COPD. It was found that FEV_1<50% of the predicted, isolation of PPM from sputum culture, and history of at least one COPD exacerbation that require hospitalization in the last year are independently associated with bronchiectasis (12). Although the prevalence of bronchiectasis was lower (4%) in the ECLIPSE cohort as compared to the other studies, number of patients with bronchiectasis increased in line with the increase in GOLD stages (20).

In a study conducted in Turkey, whilst the prevalence of bronchiectasis was found to be 31% in COPD patients undergoing mechanical ventilation, it was demonstrated that patients with bronchiectasis had higher number of respiratory illness-related hospitalization, more severe airway obstruction, higher pulmonary arterial pressure, longer duration of intensive care and hospital stay, longer period of mechanical ventilation requirement, and had higher prevalence of ventilator-associated *P. aeruginosa* pneumonia. However, this study found no relation between bronchiectasis and mortality (28).

In a recent study, Martinez Garcia et al. (13) investigated the prognostic value of bronchiectasis in patients with moderate-severe COPD. A total of 201 COPD patients participated in the study were followed up for a mean of 48 months; whilst 8 deaths occurred in 86 patients without bronchiectasis, 43 deaths occurred in 115 patients with bronchiectasis. The risk of mortality was found to be significantly increased in patients with bronchiectasis, independent from the known causes of mortality (HR: 2.54; p=0.02). Consistent with the previous studies, this study determined more frequent and severe exacerbations, higher levels of inflammation markers, and more frequent PPM isolation/colonization. Whilst *P. aeruginosa* was isolated from a total of 19 patients, 15 of these patients were positive for bronchiectasis. However, non-tuberculosis mycobacteria, which are frequently encountered in patients with bronchiectasis, were not isolated in this study.

CONCLUSION

Particularly in the most recent studies, it was determined that co-occurrence of COPD and bronchiectasis is more prevalent in patients with moderate to severe COPD, and these patients are prone to more severe and frequent exacerbations together with higher PPM colonization and inflammation level and, the most important, have a higher mortality rate. These findings suggest that HRCT scanning might be included in routine diagnostic methods in selected COPD patients (advanced stage, PPM positivity and frequent exacerbation). However, considering radiation exposure and additional expenditure brought by HRCT, studies that assess the efficacy of routine utilization of this method are needed.

In the event of concurrent chronic obstructive pulmonary disease and bronchiectasis, and considering the co-occurrence of severe disease, frequent exacerbations and PPM (especially *P. aeruginosa*) positivity it can be thought that agents such as inhaled steroids, tiotropium, azithromycin and roflumilast, which have been shown to be effective in frequent exacerbations of COPD phenotype, may have beneficial effects also in this phenotype. Likewise, inhaled antibiotics that have been shown to be effective in bronchiectasis patients with PPM positivity might have beneficial effects in this phenotype. However, longitudinal studies are needed on this subject.

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