

Bronchiectasis and Emphysema

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ABSTRACT

Emphysema is the predominant component in alpha1-Antitrypsin (α 1-AT) Deficiency, but the prevalence and impact of bronchiectasis is greater than previously recognized. Bronchiectasis is more common and severe where emphysema is seen and may add to the severity of the disease and worse health status. The pathogenetic association between bronchiectasis and emphysema is not well defined. Whether bronchiectasis take advantage of the α 1-AT augmentation therapy remains unknown. The coexistence of emphysema and bronchiectasis in COPD patients is nor rare. Bronchiectasis could have an impact on disease course over and above the effects of emphysema. From the other side, the presence of emphysema in bronchiectasis is common and may contribute to the severity of airways obstruction. Emphysema may represent a risk factor of mortality in patients with bronchiectasis.

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INTRODUCTION

According to our previous knowledge emphysema represented a parenchymal destruction while bronchial lesions were a component of chronic bronchitis. This concept has been changed.

In recent years, bronchiectasis is easily diagnosed using the high resolution computer tomography (HRCT) in clinical practice. Furthermore, more comprehensive screening of the chronic obstructive pulmonary disease (COPD) population has revealed that bronchiectasis is a prominent feature of the disease.

The prevalence of bronchiectasis is high in patients with moderate-to-severe (COPD) and it has been associated with exacerbations and bacterial colonization. Additionally bronchiectasis is associated with an independent increased risk of all-cause mortality in COPD patients¹.

Only a limited number of studies have assessed the association between bronchiectasis and in particular emphysema, a component of COPD. Furthermore there is some information on the prevalence and impact of bronchiectasis in alpha1-Antitrypsin Deficiency (α 1-ATD) emphysema.

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BRONCHIECTASIS AND α 1-ATD EMPHYSEMA

α 1-ATD is a genetic condition that predisposes to early onset pulmonary emphysema and airways obstruction. It is well known that emphysema is the predominant component of COPD in α 1-ATD, but the prevalence and impact of airway disease are greater than previously recognized. Previous reports have suggested an association between emphysema and bronchiectasis and a causal link has been postulated².

A significant proportion of patients with α 1-ATD have airway reactivity with wheezing and approximately 40% of patients deficiency have chronic cough and sputum expectoration. Dowson and coworkers have shown that patients with chronic sputum production had worse airflow obstruction, more extensive emphysema, worse health status and more exacerbations than those who did not⁽³⁾.

There is evidence suggesting that airways disease is an early and integral component of disease pathogenesis.

A possible hypothesis among the many airway- disease phenotypes described in α 1-ATD is that unopposed human neutrophil elastase (HNE) is present in both airways and the lung parenchyma. In the airways bronchial connective tissue is injured when protease inhibitor deficiency is present, since normal microbial and native airway cellular interactions may be amplified⁴. However, it is still uncertain whether bronchiectasis is a primary feature of the disease or a result of airway damage due to recurrent infection. Whether respiratory viral or bacterial infections are necessary for airways disease in AATD remains unknown.

Clinical airways disease in α 1-ATD disease is heterogeneous including asthma, chronic bronchitis and bronchiectasis.

In the NHLBI Registry study in the United States including 1129 patients, a history of asthma was reported in 35%, while clinical diagnosis was confirmed in 21% of the cohort. Reversible airflow obstruction was seen in 61% of the patients⁵.

The frequency of bronchiectasis in α 1-ATD is difficult to ascertain because the disease is relatively uncommon and varies in different studies (27-60%). There is some controversy whether bronchiectasis is a frequent clinical phenotype in take advantage of the treatment. Population based bronchiectasis registries have not shown large differences in AAT allele frequencies compared with control populations. However, more studies within α 1-ATD cohorts have shown frequent bronchiectasis⁴.

In the 14 patients studied by King and coworkers, the prevalence of bronchiectasis was 43%. Patients with

bronchiectasis had a significant higher infection score than those without. Interestingly the presence of bronchiectasis was greater in lobes in which the emphysema score was higher. An alternative explanation is that the association between emphysema and bronchiectasis may reflect a regional interaction between the underlying pathogenic processes⁶

Parr and coworkers estimated the prevalence and impact of bronchiectasis on 74 subjects with α 1-ATD (PI*ZZ). CT bronchiectasis was seen in 70 individuals (95%), whilst clinically significant disease as manifest by 4 or more segments of airway abnormality and chronic sputum production in 20 individuals (27%). Subjects with greater bronchiectasis severity had more severe emphysema. Airway disease scores correlated with health status, and bronchial wall thickening correlated with FEV1. Thus the severity of airways disease had an independent effect on health status after adjustment for severity of emphysema²

The commonest morphologic type is cylindrical bronchiectasis, although cases of varicose and cystic bronchiectasis have been described (Figure 1).

COPD exacerbations are a frequent event in α 1-ATD. This frequency is estimated by only a few studies. A large 1-year cohort in the United Kingdom, shown exacerbations in 54%⁴. Exacerbations are associated with PMN influx into the lung. These PMNs release products when activated, including HNE in proportion to the airway bacterial load⁷. There is a controversy if the augmentation therapy with α 1 AT alter the exacerbation frequency^{8,4}.

Microbiologic organisms are frequently associated with COPD exacerbations in α 1-ATD (in approximately

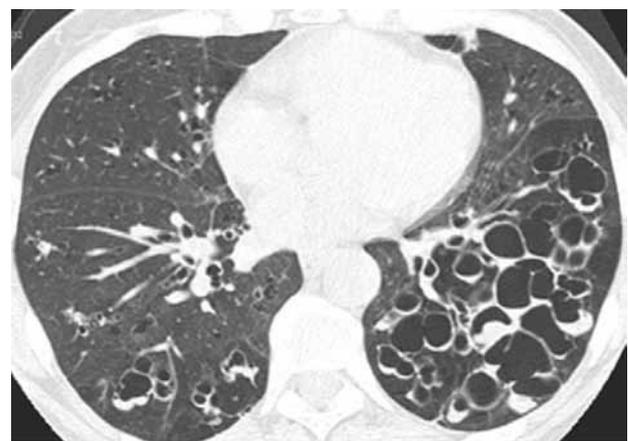


FIGURE 1. Lower zone image from a subject with α 1-ATD showing severe cystic bronchiectasis and mild emphysema. (From ref. 2 with permission).

50% of cases) with the most frequently isolated species being *H. influenzae*, *P. aeruginosa*. Much interest has been generated in whether the microbiome additionally might be causal in the genesis of COPD or some COPD phenotypes, particularly bronchiectasis⁴.

BRONCHIECTASIS AND EMPHYSEMA BEYOND α 1-ATD

In a different view, there are a few studies reporting the association between bronchiectasis and emphysema, as a component of COPD, beyond the α 1-ATD.

The coexistence of emphysema and bronchiectasis in COPD patients is not rare (Figure 2).

Fujimoto and coworkers classified 172 patients with COPD in different phenotypes according to HRCT findings. They found that 25,6% of the patients had a combination of emphysema and bronchial wall thickness. The patients of this phenotype had more cough, sputum production and wheezing, higher rate of exacerbation or hospitalization and greater reversibility of airflow limitation as compared with the emphysema phenotype⁹.

Gatheral and colleagues aimed to determine the impact of bronchiectasis on clinical outcomes in 406 COPD patients independent of coexisting emphysema. They found that bronchiectasis in COPD patients is very common (69%) and is associated with increased hospitalization and respiratory infection due to *Pseudomonas Aeruginosa* and atypical mycobacteria, independent of the severity of coexisting emphysema and bronchial wall thickness.

Bronchiectasis could have an impact on disease course

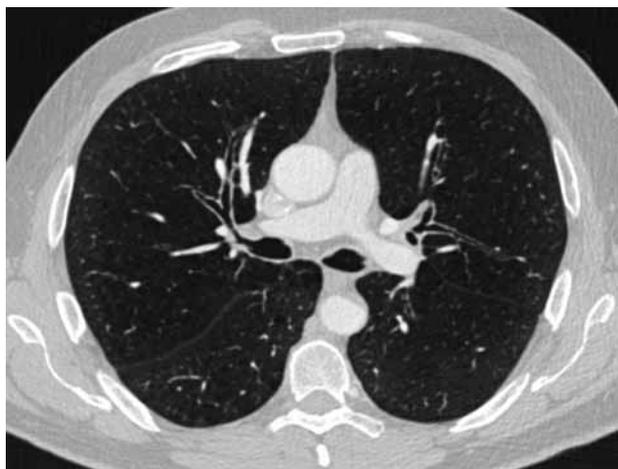


FIGURE 2. HRCT image of a 65 years-old COPD patient with emphysema and bronchiectasis.

over and above the effects of emphysema and bronchial wall thickening by impairing mucociliary clearance, causing mucus stasis and increased bacterial colonisation. This has potential important implications for therapy¹⁰.

On the other hand the presence of emphysema in patients with bronchiectasis has been sparsely reported in a few studies.

Loubeyere and coworkers in a retrospective study assessed the presence and extent of emphysema in 90 patients, non smokers, with proved bronchiectasis using the HRCT. He found a high prevalence of emphysema in patients with bronchiectasis (45%) and emphysema was mainly localized in the same bronchopulmonary segments as bronchiectasis¹¹. The presence of emphysema was in relation to the extent and to the severity of bronchiectasis.

Additionally, the group of patients with CT evidence of emphysema had significantly higher airflow obstruction and air trapping compared to the group without emphysema.

The authors suggest that may be there is a causal association between small airway disease and emphysema and that emphysematous changes are a consequence of bronchiolar inflammation.

There is evidence that emphysema may represent a risk factor of mortality in patients with bronchiectasis.

Loebinger et al had retrospectively reviewed CT images of 91 patients with bronchiectasis, revealing that increased wall thickness and emphysema were the strongest predictors for mortality in patients with bronchiectasis¹².

In a recent study Goeminne et al analyzed the risk factors for mortality in 245 patients with bronchiectasis¹³. They found that in a period of 5,18 years follow-up the overall mortality in Bronchiectasis was 20.4%. Patients with Bronchiectasis and associated COPD had a mortality of 55% in that period. The authors concluded that COPD was a risk factor related to mortality.

Another retrospective study aimed to determine the independent risk factors of 5-year mortality in 89 patients, newly diagnosed with bronchiectasis. Eight of them (9%) had emphysema as well. At the end of the study, 13.5% of the patients died. Mortality was significantly associated with emphysema and radiographic extent of bronchiectasis. Moreover, the radiographic extent of bronchiectasis and the airflow limitation in patients coexistent with emphysema was more severe than those without emphysema. Thus, the authors conclude that emphysema might be a risk factor for mortality in bronchiectasis and suggest as a possible pathogenic explanation that the presence of emphysema might be a result of the inflam-

matory response in distal airways in the development of bronchiectasis, which lead to the worsening of the lung function and prognosis¹⁴.

In conclusion

Emphysema is the predominant component in α 1-ATD, but the prevalence and impact of bronchiectasis is greater than previously recognized. Bronchiectasis is more common and severe where emphysema is seen and may add to the severity of the disease and worse health status. The pathogenetic association between bronchiectasis and emphysema is not well defined.

Whether bronchiectasis take advantage of the α 1-AT augmentation therapy remains unknown.

The coexistence of emphysema and bronchiectasis in COPD patients is nor rare. Bronchiectasis could have an impact on disease course over and above the effects of emphysema.

From the other side, the presence of emphysema in bronchiectasis is common and may contribute to the severity of airways obstruction. Emphysema may represent a risk factor of mortality in patients with bronchiectasis.

Questions to be answered, future challenges:

- Which is the pathogenetic association between bronchiectasis and α 1-ATD?
- Does Inhaled and intravenous augmentation therapy help both emphysema and airways disease in α 1-ATD?
- Which is the prevalence and the impact of emphysema in bronchiectasis?
- Does the future therapeutic approach target to both components?

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